CU6-H00632-65-P35572

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Brain

Journal of Neurology

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VOLUME LXI

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MACMILLAN AND CO., LIM
ST. MARTIN'S STREET, LO
NEW YORK : THE MACMILL
1938

P 35,572

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MARCH, 1938

BRAIN.

PART 1, VOL. 61.

INCREASED SPONTANEOUS ACTIVITY PRODUCED IN MONKEYS BY BRAIN LESIONS.

BY CURT P. RICHTER,
Psychobiological Laboratory, Henry Phipps Psychiatric Clinic

AND

MARION HINES,
Department of Anatomy, Johns Hopkins University, Baltimore, Md.

THE rôle played by the frontal lobes in the regulation and control of spontaneous activity is still a subject of dispute. Ferrier (1876), Bianchi (1922), Lashley (1920), Jacobsen (1931 and 1936), and Levin (1936), found that removal of the frontal lobes in animals (dogs, monkeys and rats) resulted in restlessness and increased activity, while Goldstein (1927) and Kleist (1934) reported that destruction of the frontal lobes in man by tumours or war injuries resulted in apathy and decreased activity. Brickner (1934) reported increased restlessness in a patient with surgical removal of both frontal lobes.

All these experimental and clinical observations were made incidentally to other studies and were handicapped by the lack of adequate means of measuring activity. The clinical work was further handicapped by the lack of definite knowledge regarding the exact localization of the lesions.

These limitations have been overcome, at least in large part, in the following experiments in which the effects produced on the activity of monkeys by definitely circumscribed brain lesions were studied by means of a special cage equipped with a recording device for measuring activity. A brief report of these experiments was given at the Second International Neurological Congress in London, in 1935 (Richter and Hines).

METHODS.

A photograph of one of the cages used in these experiments is shown in fig. 1. These cages were 6 ft. long, 6 ft. high and 18 in. wide. The monkey's movements around a central rod which served as an axle were recorded. One end of the rod was connected by gears to two cyclometers on the outside of the cage, and the other end extended freely through a small hole in the opposite side. Every tenth of a revolution of the axle in either direction was recorded. One end of a thin flexible steel rod, 2½ ft. long, was clamped to the axle, the other was connected by a 9-in. length of swivel chain to the collar of the monkey. Thus, the animal could reach every corner of the cage, could sit on either of two platforms, one over the central axle, and the other in one corner just above the floor, and still have all of its activity recorded except for a small amount within the range of the chain at the end of the flexible rod. The two cyclometers were read daily.

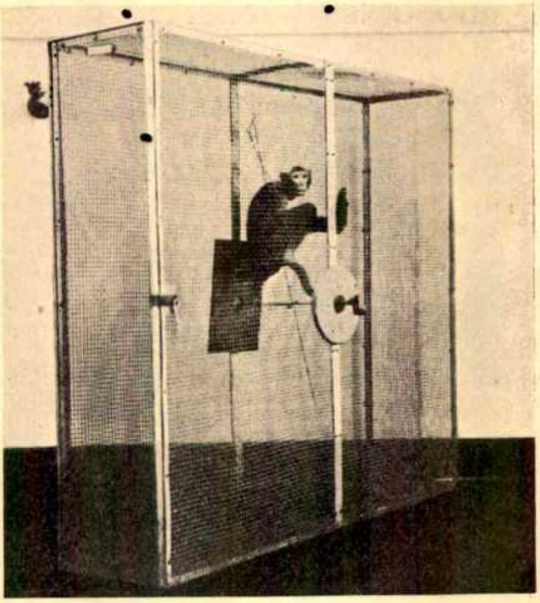


FIG. 1.—Cage used for measuring activity of monkeys.

The room was maintained at a fairly constant temperature, 70° to 80° F., and as free as possible from noise. The animals were fed at 7.30 in the morning just before the cages were cleaned, and again late in the afternoon. The food consisted of bread, carrots, sweet potatoes, cabbage, lettuce and milk.

The brain operations were performed several weeks after the animals were placed in the cages, when it was certain that a constant level of activity had been attained.

In the preliminary experiments the brain tissue was removed by suction through a small glass cannula, while in later experiments the tissue was removed with a cataract knife and preserved for histological study. At the conclusion of the experiments the animals were killed, the brains were removed, fixed in formalin and preserved for macroscopic and microscopic study. Most of the brains were sectioned and stained with Spielmeyer's modification of Weigert's technique; the rest were studied only macroscopically.

Nineteen monkeys used in the experiments were subjected to a total of forty-six operations.

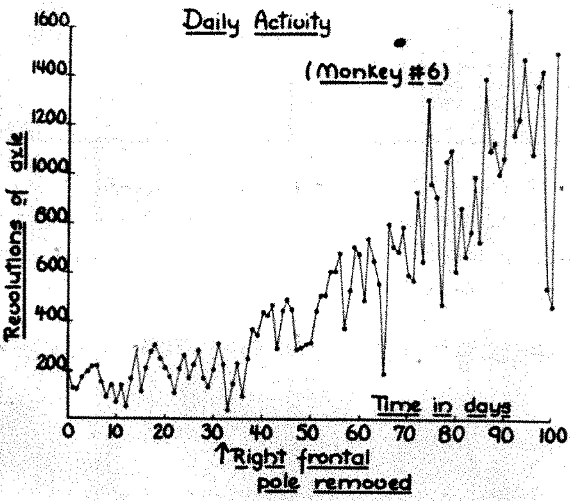


FIG. 2.—Graph showing increase in activity produced by gross removal of the right frontal pole of the brain. Ordinate: Activity in revolutions around axle of cage. Abscissæ: Duration of experiment in days.

RESULTS.

Effect Produced by Gross Removal of Frontal and Occipital Poles.

In the preliminary experiments undertaken for purposes of orientation, a study was made of the effects produced by gross removal of the frontal and occipital poles of the brain.

The record from one of these animals with a unilateral removal of the right frontal pole is shown in fig. 2. It will be seen that the activity increased from a level near 200 revolutions per day to a level near 1,200 and the increase appeared to be permanent.

The frontal poles were removed unilaterally in five animals; in two of these the other frontal pole was removed at a second operation. The results are summarized in Table I. An increase in activity was produced by unilateral as well as bilateral operations in all of the animals. In two animals in which the unilateral operation had produced only a small increase, a large increase was produced by the subsequent removal of the other pole.

TABLE I.—GROSS REMOVAL OF FRONTAL POLE.

MONKEY NO.	AVERAGE DAILY ACTIVITY IN FULL REVOLUTIONS OF AXLE						NUMBER OF DAYS OBSERVED AFTER FIRST OPERATION
	10 days before first operation	10 days on plateau after operation	Highest peak after operation	10 days before second operation	10 days on plateau after operation	Highest peak after operation	
6	214	1,142	1,674	—	—	—	88
38	109	295	535	—	—	—	50
57	130	360	545	—	—	—	97
4	68	95	173	95	424	731	67
46	71	224	313	224	397	725	112
PREFRONTAL CORTEX REMOVED.							
49	96	126	205	126	564	824	65
70	57	136	210	136	935	1,453	124

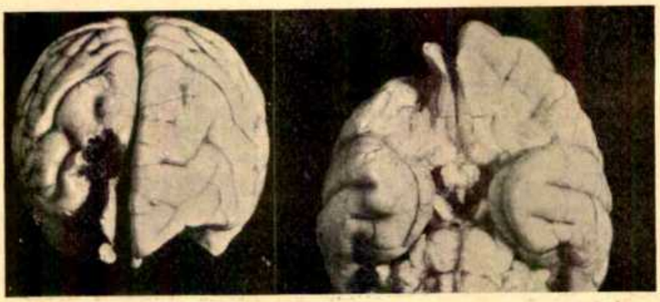


FIG. 3.—Frontal and dorsal views of brain of animal showing unilateral frontal pole lesion which produced marked increase in activity (*see* fig. 2).

The extent of the lesion in the animal whose record was shown in fig. 2 may be seen in the photograph of the frontal and ventral views of the removed brain in fig. 3.

Histological study of the brains of the five animals showed that the lesions were limited to the prefrontal cortical Areas 8, 9, 10, 11 and 12, and to the anterior ends of the caudate and putamen.

Unilateral and bilateral removal of a large area in the occipital region in two animals produced a slight decrease rather than an increase.

Unilateral or bilateral removal of Area 6 alone in two animals also was without effect. Combined removal of Area 6 and the prefrontal cortex in two animals had no effect; it did not produce "marked torpor" or "sluggish motor behaviour" as reported by Fulton, Jacobsen and Kennard (1932).

Effect Produced by Removal of the Entire Prefrontal Cortex Sparing the Striatum.

Further experiments with definitely circumscribed lesions were then undertaken to determine the rôle played (1) by the prefrontal cortex and (2) by the underlying striatum.

Unilateral removal of the prefrontal cortex produced only a slight increase in the two animals operated on; however, subsequent removal of the other prefrontal cortex produced a large increase in activity (*see* Table I). In the record of one of these animals shown in fig. 4, removal of the prefrontal cortex on one side produced an increase from an average level of 57 to 136 revolutions, and removal of the other cortex an increase to an average level of 935 revolutions. The overactivity appeared to be permanent.

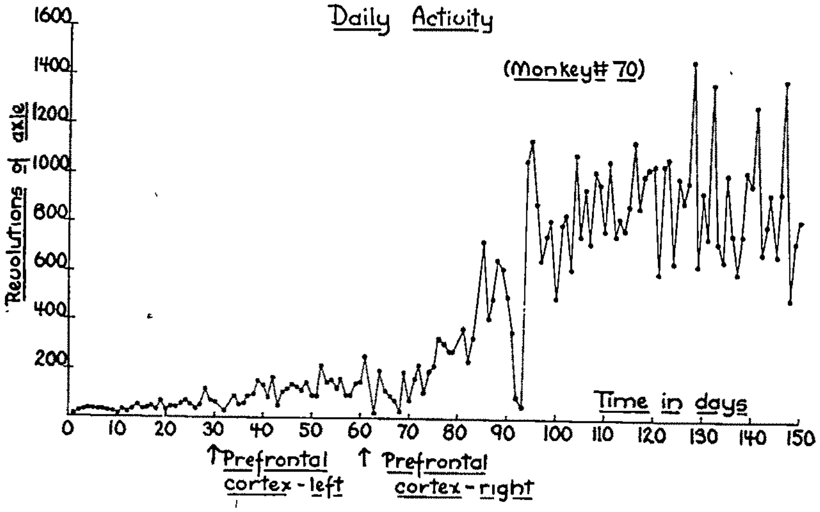
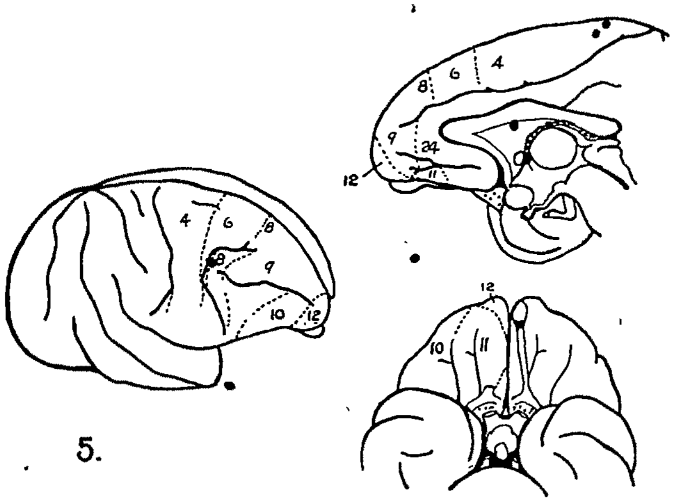


FIG. 4.—Graph showing effect produced on activity by removal of one prefrontal cortex and subsequent removal of the other prefrontal cortex.

The limitation of these lesions to the prefrontal cortex was established by histological studies of the brains and of the extirpated tissue.

It would seem likely then that spontaneous activity is controlled at least in part through the prefrontal cortex, in agreement with the observations made by Jacobsen (1931 and 1936), and Fulton, Jacobsen and Kennard (1932).



5.

FIG. 5.—Drawing showing cortical areas of frontal lobes. The lines on these charts indicating the boundaries of Brodmann's areas are not definitely fixed. The field which has in the writers' investigations shown the greatest variation is the dorsal extension of Area 8. Sometimes the dorsal extension of Area 8 is very slender and sometimes several millimetres in breadth.

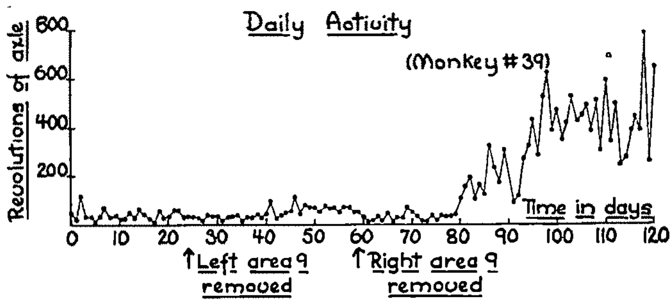


FIG. 6.—Graph showing the effect produced on activity by removal of Area 9 on one side and subsequent removal of Area 9 on the other side.

Effect of Separate Removal of Areas 8, 9 *and* (10, 11 *and* 12).

Having thus shown that activity could be increased by bilateral removal of the entire prefrontal cortex it was decided to determine whether the same large increase could be obtained by bilateral removal of any of the individual parts, as of Areas 8, 9 or (10, 11 and 12) shown in fig. 5.

It was found, in agreement with the results just reported, that unilateral removal of any one of the prefrontal areas produced only a slight, if any, increase in activity. Bilateral removal of Areas 8 or (10, 11 and 12) also had very little effect. Bilateral removal of Area 9 produced a definite increase, as may be seen in the record of one of the animals shown in fig. 6. The average daily activity before operation was 41 revolutions, after unilateral removal of Area 9, 67 revolutions, and after the bilateral removal, 441.

The results of these experiments are summarized in Table II. It will be seen that in one animal unilateral removal of Area 8 had no effect on activity and bilateral produced a small decrease. Areas (10, 11 and 12) were removed in two animals. Unilateral removal produced a small increase in one; bilateral removal had no effect in one and produced a decrease in the other. The small increase after the unilateral removal in one of the animals can be explained by the fact that the activity was increasing at the time the operation was performed. Unilateral removal of Area 9 produced a small increase in one of two animals and bilateral removal produced a definite increase in both.

TABLE II.—SEPARATE REMOVAL OF AREAS (8), (9), (10, 11, AND 12).

MONKEY NO.	AVERAGE DAILY ACTIVITY IN FULL REVOLUTIONS OF AXLE		
	10 day period before first operation	10 day period after unilateral removal	10 day period after bilateral removal
(AREA 8)			
66	140	144	102
(AREAS 10, 11 AND 12)			
66	102	97	39
63	110	190	198
(AREA 9)			
39	41	67	441
67	160	121	224

Effect Produced by Injuries to the Striatum.

The fact that such a great increase in activity was produced in animals with the gross unilateral removal of the frontal pole involving both the prefrontal cortex and the tip of the striatum, while no increase or only a slight increase was produced by the unilateral removal of the cortex alone, indicated that the striatal injuries must also play an important part.

In order to determine the rôle played by the striatum in the production of overactivity the following experiments were performed. First, an attempt was made to make unilateral lesions in the tip of the striatum without injuring the cortex. These efforts were unsuccessful, due to our inability to localize the lesion and to remove a sufficiently large piece of the striatum. In later experiments the prefrontal cortex was removed unilaterally in one operation. Several weeks later, when it was certain there would be no increase in activity from this operation, the tip of the striatum was removed. It was found that such striatal lesions regularly produced an immediate and great increase. In the record of one of these animals in fig. 7 it will be seen that in contrast to the small increase (from an average level of 38 revolutions to 145 and 145 to 184) produced first by removal of Areas 10 and 11 and then by removal of all of the prefrontal cortex anterior to Area 8, a very great

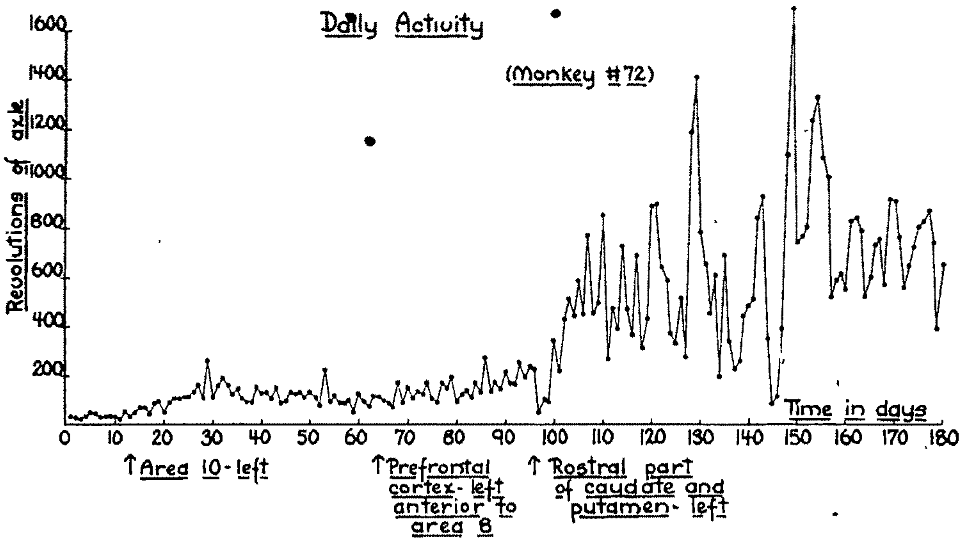


FIG. 7.—Graph showing effect produced on activity by unilateral removal of the tip of the caudate and putamen subsequent to removal of Areas 9, 10 and 11.

increase (to 1,057) was produced by subsequent removal of the tip of the striatum (*see* Table III).

Similar records were obtained in two other animals as may be seen in Table III. In monkey No. 69 the small increase from an average level of 199 to 322 revolutions was produced by unilateral removal of left Areas 9 and 10, and a very large increase from an average level of 322 to 828 by subsequent removal of the tip of the caudate and putamen. Removal of Areas 9 and 10 and the tip of the striatum on the other side produced an additional increase. Macroscopic and histologic studies made on this brain showed that Areas 9 and 10 and the tip of the striatum had been removed on both sides.

TABLE III.—INJURIES TO THE STRIATUM.

AVERAGE DAILY ACTIVITY IN FULL REVOLUTIONS OF AXLE.

MONKEY NO. 72		MONKEY NO. 69		MONKEY NO. 71	
10 day period before 1st operation	38	10 day period before 1st operation	199	10 day period before 1st operation	103
10 day period on plateau after removal of Areas 10 and 11 on left	145	10 day period on plateau after removal of Areas 9 and 10 on left	322	10 day period on plateau after removal of left Area 9 and lateral Area 10	229
10 day period on plateau after removal of entire prefrontal cortex on left anterior to Area 8	184	10 day period on plateau after removal of tip of caudate and putamen on left	828	10 day period on plateau after removal of tip of caudate and putamen on left	393
10 day period on plateau after removal of rostral part of left caudate and putamen	1,057	10 day period on plateau after removal of entire prefrontal cortex and tip of caudate on right	929	10 day period on plateau after removal of prefrontal cortex on right	632

In monkey No. 71 activity increased from an average of 103 revolutions per day before removal of Area 9 and the lateral part of Area 10 to a level of 229. Subsequent removal of the tip of the caudate and putamen produced an increase to 393 revolutions. Removal of the prefrontal cortex on the opposite side produced an increase to 632.

REMARKS.

It was found that in general the increase in activity was much more precipitous in animals with striatal lesions than in animals with lesions limited to the cortex. Thus, in the record (fig. 7) of an animal with a striatal lesion the activity showed an increase three days after operation and reached a plateau after six days; in the record (fig. 4) of an animal with cortical lesions, activity did not increase until fifteen days after operation, and then only very gradually, not reaching a plateau until thirty-five days later.

HISTOLOGICAL STUDY OF BRAINS.

The degeneration of fibres and nuclei was studied in detail in three animals with cortical and striatal lesions. A short summary is given below.

Monkey No. 72 (*lesion of the left prefrontal cortex, head of the caudate and putamen*).

The lesion was well circumscribed; it encroached in no way upon Areas 4 or 6, and left in place only the caudal limbs of the infraorbital gyri. The dorsal surfaces of the anterior end of the left caudate and putamen were clearly removed without injury to the globus pallidus. The loss of fibres in the external capsule was great and extended caudally to the level of the middle of the globus pallidus. The loss of fibres in the corpus callosum was confined to its most anterior part, involving little more than the genu. The greatest reduction of fibres in the internal capsule was found medially. Also the number of fibres within the deep layers of the small remnant of the ventral surface of the cortex, i.e. the caudal limbs of the gyri orbitalis and frontalis inferior, was fewer than in similar positions on the normal right side.

The left medial nucleus of the thalamus was definitely smaller than the right and there was perhaps a slight reduction in the lateral nuclear group also. Further, in this brain, where no injury was done to the right side, the reduction of the nerve fibres within and on the ventral border of the lateral division of the left anterior nucleus was particularly clear. There was a definite reduction in the anterior thalamic peduncle, in the fibres which enter the mediodorsal part of the globus pallidus and the medial part of the substantia nigra, and in the stratum sub-callosum.

Although in this brain, as in the others, it was not possible to trace the route taken by the tractus cortico-tegmentalis, nevertheless comparison of the density of fibres both in the thalamus and in the midbrain tegmentum showed clearly a loss on the left medial to the general subthalamic region and lateral to the nucleus ruber, respectively. At the level of the oculomotor nucleus the loss of fibres was obviously confined to the medial part of the basis pedunculi This loss could be traced into dorsomedial parts of the medial group of descending fibre bundles in the pons, where it gradually disappeared. A search of the midtegmental region caudal to the nucleus ruber revealed what might be considered a scattered loss of fibres dorsal to the main body of the lemniscus systems, and also dorsolateral to the lateral group of tegmental nuclei. In the medulla oblongata at the caudal level of the superior olive, no loss of nerve fibres within the pyramids could be seen, and at this level there was no visible loss of fibres within the tegmentum.

The only fibre degeneration which seemed to be located definitely within the body of the basal ganglia was observed among normal appearing bundles which lie well outside the internal capsule, within the nuclear mass of junction between the caudate and the putamen. These partially degenerated bundles can be followed caudally to the level of the anterior commissure.

The right hemisphere was intact and no disturbance of its blood supply in the region opposite the lesion could be seen.

Monkey No. 69 (*bilateral removal of Area* 9 *and lateral part of Area* 10 *and head of caudate and putamen*).

The diminution of the number of nerve fibres in both the capsula externa and the capsula extrema extended on either side as far caudally as the level of the mid-region of the Island of Reil. There was a reduction of fibres in the subcallosal bundle and in the internal capsule, and in the medial and ventral part of the anterior thalamic peduncle; but within the corpus callosum the reduction was confined to a scattered degeneration within the dorsal part of the genu. The reduction within the internal capsule was circumscribed and confined to the medial division. The more mediodorsal bundles strayed from the internal capsule and at the level of the midthalamic region lay dorsomedially of the corpus subthalamicum and medioventrally of Forel's Field H_2, forming perhaps a tegmental projection system, which, with this technique, could not be traced further than the general subthalamic region. Within the midbrain, the tegmentum dorsolateral to the necleus ruber, a scattered diminution in density of staining appeared.

From the fact that the medial part of the internal capsule swings ventrally to lie on the ventral surface of the midbrain as the pes pedunculi, it followed that the more medially lying concentration of fibre loss was seen in the dorsomedial part of the rostral division of the substantia nigra. This loss involved about the medial one-third of the fibres entering the substantia nigra on the left and not more than the medial one-fourth or one-fifth on the right at homologous levels. At the level of the exit of the root of the third nerve no loss or diminution of nerve bundles could be demonstrated in the substantia nigra. No decrease of fibre content within the globus pallidus was observed.

On the left, the remaining loss in the pes pedunculi was confined to the most medially lying fibres. This loss could be followed into the pontine levels as one in the most dorsomedial bundles. On the right, a very slight loss was seen. Caudal to the mid-pontine region, none could be identified on either side. At the level of the pyramids, the sections of this brain appeared to be normal throughout.

Monkey No. 71 (*removal of all the prefrontal cortex anterior to Area* 8 *and the head of the caudate and putamen on the left side, and of Area* 9 *and the lateral distribution of Area* 10 *on the right*).

The loss in fibre content of both the capsulæ externa and extrema showed a marked gradually decreasing decrement as far caudally as the Island of Reil. A similar gradually decreasing decrement in the number of degenerated fibres found in the deep white matter of the ventral aspect of the hemisphere was followed from the rostral part of the lesion to the mid-transverse plane of the hemisphere. The loss within the corpus callosum was confined to the region of the genu.

The loss of fibres within the anterior limb of the internal capsule was roughly estimated to be about one-fourth of the total on the right and about nine-tenths on the left. Consequently, the attempt at removal of the head of the caudate was equivalent to cutting both the corticifugal and the corticipetal fibres anterior to the subcortical lesion. Although the actual cortical lesion itself was well confined, the total lesion on the left was practically equivalent to removal of the prefrontal area, anterior to Area 8.

Comparison of degeneration of fibres into the thalamus showed that those on the left were greater in number than those on the right. This loss, visible bilaterally, was followed easily into the ventral part of the lateral group and medial nuclei, and on the left, possibly into the caudal part of the anterior nucleus. There was perhaps a slight decrease in the number of nerve fibres within the lateral nucleus on the left side.

In the level of the subthalamus, on the left, many of the degenerated fibres no longer lay within the confines of the internal capsule, but rather in the thalamic tegmentum itself, ventramedially to Forel's Field H_2. Not all of these fibres could be followed rostrally into the midbrain tegmentum (*see* Levin, 1936), and they formed therefore (if this technique is reliable) a projection system into the sub-thalamic tegmentum. Others of these degenerated fibres on the left were followed through many sections, lying lateral to the ganglion interpedunculare. They did not apparently penetrate this nucleus, but gradually disappeared as their destination was sought caudally, forming possibly a projection system into the ventral midbrain tegmentum. Besides this diminution in number of nerve fibres within the ventral part of the midbrain tegmentum there is a scattered loss of stained myelin sheaths within the tegmentum dorsolateral to the anterior reaches of the left nucleus ruber. Further within the dorsal and medial part of the medial division of the globus pallidus there is an apparent decrease in the number of stained myelin sheaths.

In the level of shift of the fibre bundles from a position within the internal capsule to one within the pes pedunculi, the degeneration on the left was confined to the medial fourth, that on the right to a few medially placed bundles. These degenerated fibres left this position in two directions, some shifting dorsally to the medial third of the substantia nigra, others into the medial part of the mediodorsal bundles in the pons.

The subcallosal bundle was greatly degenerated on the left, for on that side it was interrupted in the removal of the rostral caudate-putamen complex. On the right the degeneration of the subcallosal bundle appeared to be as great as on the left as far caudally as the level of the rostral end of the globus pallidus. From this level caudally some normal fibres were found on both the right and on the left.

In summary, the analysis of the fibre degeneration within these brains subjected to removal of the rostral divisions of the caudate or of the putamen did not, with one exception, reveal any projection system not previously recognized by the recent studies of corticifugal systems arising in various portions of the prefrontal cortex (Mettler, 1935; Levin, 1936). This exception was the bundle of degenerating fibres (brain of No. 72) found within the remaining part of the caudate, which could be followed caudally in the ventromedial wall of the telencephalon to be lost in the region ventral to the anterior commissure. That these degenerated fibres actually had their nuclei of origin within the nucleus is doubtful because they could not be identified as degenerated in the brains of Nos. 71 and 69. More likely they were fibres of passage which arose within the medial surface of the frontal lobe.

All three brains have in common great fibre degeneration within the long association systems, such as the capsule externa and extrema, as well as within the subcallosal bundle. In all of these the anterior thalamic peduncle shows great loss of fibres, the greatest in the brains which had suffered the greatest cortical or striatal removals. The greatest diminution in size of thalamic nuclei was found, as should be expected, in the dorsal part of the medial nucleus (Clark and Boggon, 1935; Walker, 1936). The loss of nerve fibres about or within the anterior thalamic nucleus was confined to brains Nos. 71 and 72. (Brain of No. 69 had suffered neither loss of the infra-orbital gyri nor interruption of their interregional connections.)

The degeneration of projection systems other than the anterior thalamic peduncle, common to all three of these brains, are those which apparently terminate within the diencephalic tegmentum[1] and the mesencephalic tegmentum, and those which can be traced into the substantia nigra and into the dorsomedial part of the pons. Degeneration of fibres into the globus pallidus was very definite in the brain of monkey 72 from which the prefrontal area had been removed (*see* Mettler, 1935; and Levin, 1936).

That no specific loss of nerve fibres could (with the use of this technique) be allocated to the striatal injuries was disappointing.

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[1] Mettler (1935) was able to trace descending degeneration from the prefrontal cortex (judging by the position of the lesion it may have encroached slightly upon Area 6) into the corpus subthalamicum itself and Levin (1936) found no degenerating fibres terminating within the subthalamic tegmentum unless Areas 4 or 6 were included within the area of cortical lesion. One thing is certain, Areas 4 and 6 were not injured in these brains; nevertheless small degenerated groups of nerve fibres were seen within the diencephalic tegmentum, and could be traced no further. Of course, Spielmeyer's technique is not the best method to demonstrate the termination of degenerated fibres. The use of the Marchi technique was out of the question for these brains.

DISCUSSION.

The results of these experiments have brought definite proof of the regulation or control of activity through the frontal poles of the brain, in agreement with the observations made incidentally to other experiments by Lashley (1920), Jacobsen (1931, 1936), and others. They have brought out the fact that the striatum as well as the prefrontal cortex is concerned and that Area 9 of the cortex of Brodmann plays the most important part. This result is not in agreement with the conclusions of Kennard and Ectors (1937). They reported that animals with one hemisphere removed showed "forced" circling movements and deviation of the eyes toward the side of the lesion; and that removal of Area 8 was solely responsible for the "forced" circling movements inasmuch as removal of the occipital cortex and other prefrontal areas failed to give the same results. These observations led them to conclude that the increased activity which they observed was due to removal of Area 8. The small size of Area 8, as well as the great variation in its extent, add to the difficulties of making lesions which do not include other areas. The simple fact that it is possible to obtain a great increase in activity following an ablation of the prefrontal cortex without including Area 8 (monkey No. 39 showed a very definite increase in activity after bilateral removal of Area 9, completely sparing Area 8; and monkeys Nos. 69 and 71 showed increased activity after the striatal lesions were made subsequent to the ablation of Areas 9 and 10, completely sparing Area 8) suggests that the activity described in this paper is a phenomenon quite separate from that described by Kennard and Ectors as "forced" circling movements. The animals under consideration here were seen to circle only when kept in small cages. In larger cages, they were observed to walk back and forth upon the shelves, or to jump up and down from the floor to the sides of the cage. That our one case of bilateral removal of Area 8 (No. 66) did not show "forced" circling may be due to an undetermined slight difference in the operations performed; for the inclusion or exclusion of an apparently insignificant amount of cortical tissue at certain strategic places makes a great deal of difference in the sequelæ of the operation.

The mechanisms involved in the production of the increase of activity due to prefrontal and striatal lesions are not known. Viewed from a behaviour level the increased activity might be due to a change in the animal's disposition manifested in an increased desire to escape. We were unable to detect changes of such a nature. An increased hunger or thirst, if present and unsatisfied, might produce the increased activity. Our animals did not show a noticeable increase in appetite or thirst (no measurements were made). Furthermore, they were never without food or water. Still another possibility is that we are dealing with a perseveration tendency; in other words, that once started running about the cage the animal is unable to stop. However, we could not discover the manifestations of any other perseveration tendencies. For example, the animals did not continue to make chewing movements after the food was swallowed. Viewed from a more strictly physiological angle the increased activity may be regarded as a result of a release phenomenon, that is, the removal of the inhibitory influences from the higher centres may permit external stimuli to pass on freely without hindrance or inhibition to lower reflex centres. Actually the animals did show a greatly heightened distractability, responding to all kinds of stimuli.

In spite of the increase in our understanding of the nerve-fibre relations between the prefrontal cortex and subcortical centres, the exact nervous mechanisms which are involved in the production of an increase in spontaneous activity are unknown. The cortical and striatal ablations described in this paper interrupt simultaneously the corticifugal and the corticipetal connections alike. Further, there is no way to distinguish between the results of interruption of projection systems which discharge into the sensory nuclei of the thalamus from those which discharge into the motor nuclei of the general brain-stem (globus pallidus, the substantia nigra, the pons nuclei and the tegmentum of the subthalamus, midbrain and medulla oblongata).

The fact that the increase in activity was usually delayed after cortical lesions but appeared almost immediately after striatal lesions is difficult to explain. It occurred to us that the greater delay in the increase resulting from cortical lesions as compared with the striatal lesions might be due to the fact that the cortical lesions were bilateral and produced a greater shock due to the greater amount of extirpated cortical tissue. However, a strikingly sharp increase was shown in an animal after bilateral removal of prefrontal cortex and of the tip of the striatum. In this animal the removal of the prefrontal cortex of both sides did not prevent the appearance of a sudden increase in activity.

The fact that the same operation produced unequal increases in activity in different animals, and also that unilateral lesions produced a larger increase than bilateral lesions in some animals, may possibly be explained in terms of the greater variation of a phylogenetically newer system. Of course, the condition of the animals, as well as the animals' adjustment to the cage and the surroundings, may play an important part in modifying the results.

SUMMARY.

(1) Permanent overactivity was produced in five macaques by gross unilateral or bilateral removal of the frontal poles of the brain.

(2) These lesions included the prefrontal cortex and the tip of the caudate and putamen.

(3) Unilateral removal of the prefrontal cortex in two animals produced only a slight increase in activity. Subsequent removal of the other prefrontal cortex produced a great increase.

(4) Unilateral and bilateral removal of Areas 8, or of 10, 11 and 12 in two animals, had little or no effect on activity.

(5) Bilateral removal of Area 9 produced a definite increase in activity in two animals.

(6) Overactivity was definitely produced in three animals by removal of the tip of the caudate and putamen after the previous removal of the prefrontal cortex on the same side had failed to produce an increase.

(7) It was concluded that activity is definitely controlled through the prefrontal cortex, particularly Area 9, and also through the striatum.

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SPONTANEOUS HÆMATOMYELIA: A SHORT REVIEW AND A REPORT OF CASES ILLUSTRATING INTRAMEDULLARY ANGIOMA AND SYPHILIS OF THE SPINAL CORD AS POSSIBLE CAUSES.[1]

BY J. CLIFFORD RICHARDSON.

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(1) INTRODUCTION.

Hæmorrhage holds one of the leading positions amongst the causes of disease in the nervous system. Hæmorrhage into the spinal cord is decidedly rare, in contrast with the frequent occurrence of cerebral hæmorrhage. This has been explained by the fact that the spinal arteries are long, narrow and tortuous, being subjected to less severe pressures than the cerebral vessels (Williamson, 1911). The clinical picture of intraspinal hæmorrhage, spinal apoplexy, was first described as an entity comparable to cerebral hæmorrhage early in the nineteenth century. The term "hématomyélie" was introduced by Ollivier d'Angers (1827).

The usual conception of hæmatomyelia is that of a large intramedullary spinal hæmorrhage with a tendency to spread longitudinally over several segments. It has been further designated as "tubular" and as "annular" hæmatomyelia. The hæmorrhage shows a marked predilection for the grey matter, a fact that seems adequately explained by the looser texture and greater vascularity of the grey substance as compared with the white. The posterior horns are invaded more often than the anterior horns. Experimental proof of a tendency to spread in grey matter mechanically has been provided by the experiments of Goldscheider and Flatau (1897) and of Lépine (1900), in which fluids were injected under pressure into spinal cords.

The causes of hæmatomyelia are multiple. Most authors state that trauma is much the commonest of these. A second large group is that termed "spontaneous hæmatomyelia," which includes these cases of primary hæmorrhage without trauma. Hæmatomyelia has been described as occurring secondarily in syringomyelia, intramedullary spinal tumours, syphilitic myelitis, hæmorrhagic diatheses, arteriosclerosis, miliary aneurysm of the spinal arteries (Hebold, 1885), and in acute myelitis. Smaller hæmorrhages of no clinical significance may occur in some of the above conditions, in acute anterior poliomyelitis, and in general acute infections and intoxications. The classification followed by Gowers (1886), and by Doerr (1906-7) in his comprehensive review is: (1) Traumatic. (2) Spontaneous. (3) Secondary (tumour, syringomyelia, &c.). (4) Accessory (small hæmorrhages not giving rise to any clinical symptoms). This last group should probably not be included under the term "hæmatomyelia" with its customary, though arbitrary, meaning of a large central hæmorrhage.

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[1] From the National Hospital, Queen Square, London.

Arteriosclerosis and hypertension, which are of such prime importance in cerebral hæmorrhage, have been shown to play little or no part in the ætiology of hæmatomyelia. The age incidence of the latter is earlier than that of cerebral hæmorrhage, being commonest in the twenties. Men are much more commonly affected than women. In Doerr's review of thirty cases with autopsies, there were twenty men and ten women.

Age in Years ..	0-10	11-20	21-30	31-40	41-50	51-60	61-70
No. of Cases ..	1	6	11	5	1	2	4

This report is particularly concerned with the "spontaneous" type of hæmatomyelia. On account of the great rarity of the condition, and of the uncertainty of data in many previous writings, the subject is one of many conflicting views. Gowers commented on the need for an accumulation of more exact observations, and the need still remains. More detailed considerations of ætiology will be discussed after the case reports.

(2) CASE REPORTS.

Descriptions of four cases of hæmatomyelia follow, three with post-mortem findings, and one clinical report of a non-fatal case.

Case 1.—*Hæmatomyelia caused by an angioma. A young man, aged* 25, *who was a patient in the National Hospital, under the care of Dr. Hinds Howell, from November* 19, 1936, *until his death on December* 13, 1936.

Clinical History.—He was well until October 1, seven weeks before coming to hospital. At that time he noticed a gradual onset of numbness in the toes and in the ball of his right foot. There was a tingling sensation whenever he put his foot to the ground. During the first week the numbness gradually spread upwards to involve the whole foot; then in another fortnight the back of the right leg and the inner surface of that knee also felt numb. One week after the onset of symptoms he began to have a constant dull ache across his back in the lumbar region, which was aggravated particularly by bending his head forwards. In the fourth week he began to have an intermittent slight weakness of his right leg. On October 31 he found while playing football that he could not run or kick as well as usual. The next day his legs and back were stiff and painful. On November 2nd the pain in his back and legs increased and kept him awake all that night. In the afternoon he vomited several times and there was a rapidly progressive weakness of his legs so that by evening he could not stand. On November 4 the legs were completely powerless and anæsthetic. The pain had then disappeared from his legs but remained severe in his back. He had complete retention of urine and fæces. From that time, that is for two weeks before coming to hospital, he remained in the same condition.

His past health had been good. Two weeks before the onset of his illness he had an infected scratch on his left forearm, which discharged pus in small amounts for several weeks. He also developed a large pustule on the left index finger three weeks before admission.

Clinical examination.—He was a tall muscular young man, whose legs were paralysed, and who was obviously in great pain. The cranial nerves were normal except for a fine nystagmus on full lateral deviation of the eyes. He was unable to sit up, and on trying to do so there was a deviation of the umbilicus upwards and to the left. The legs were flaccid and completely powerless. The tendon reflexes were normal in the arms, absent in the legs. There was no response to plantar stimulation. The right upper abdominal reflex was feeble, the right lower absent; those on the left were both normal. All forms of sensation were absent below the 12th thoracic segmental level on the right and the 1st lumbar level on the left. A higher band of moderately impaired sensation to pin-prick and heat and cold was present between the 5th and 9th thoracic levels on the right, with a band of hyperalgesia between it and the region of complete loss (fig. 1). There was a fairly pronounced tenderness over the lower lumbar vertebral spines. Both knee joints were swollen and contained fluid.

The temperature at first was normal except for occasional rises to as high as 100° F. There was no leucocytosis or anæmia (R.B.C. 5,200,000 per cu. mm.; Hb. 95 per cent.: W.B.C. 7,600 per c.mm.). The urine contained many pus cells. The cerebrospinal fluid was clear, colourless and under normal pressure, with no signs of block on jugular compression. Cells were not increased in number. Total protein was raised to 0·09 per cent., and the Pandy test was weakly positive. The Lange gold curve was 0000110000. The Wassermann reaction was negative in the cerebrospinal fluid and blood.

Summary.—A young man who had gradual onset of numbness and later weakness of his right leg for four weeks, then sudden severe pain in the legs and back, followed by complete paralysis of legs, bladder and bowel. Examination suggested a complete transverse lesion of the cord at about the first lumbar segment, with a higher intramedullary lesion from 5th to 9th thoracic segmental levels.

A provisional clinical diagnosis of acute myelitis was made, but as he had at the time of onset of his symptoms a purulent infected wound of his left forearm, and later developed a large pustule on the left index finger, the possibility of a staphylococcal abscess in the epidural space could not be ruled out. An exploratory laminectomy was therefore performed, with a negative result.

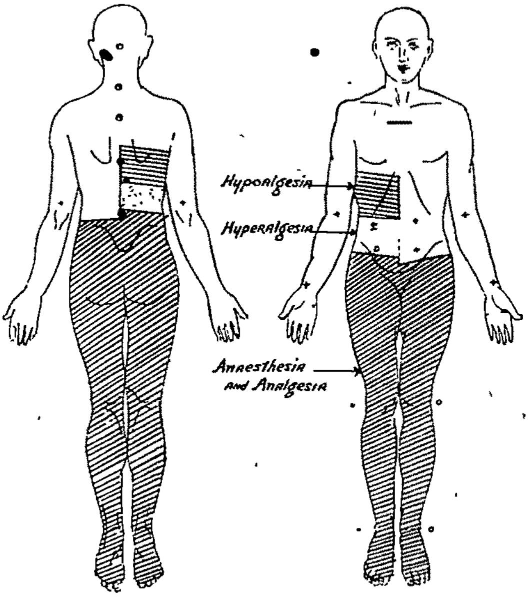

FIG. 1.—*Case* 1. Chart of sensation showing the upper band of impaired sensation to pin-prick, heat and cold on the right side from Th.5 to Th.9, and complete loss of all forms of sensation below a level of Th.12 right, and L.1 left. Tendon reflexes are indicated.

He became progressively worse owing to an intractable infection of the urinary tract. He developed high fever and a mild toxic jaundice before his death on December 13.

Post-mortem examination.—Autopsy showed the cause of death to be an acute suppurative pyelonephritis with a gangrenous cystitis.

On the surface the spinal cord looked normal except for slight diffuse swelling in the lumbar enlargement. On sections the cord showed a rounded, tubular cavity containing blood-clot, running down from the lower part of the 4th dorsal segment to the lower end of the cord. Above, the cavity was small, and situated in the right posterior horn. Lower, at the junction of the 9th and 10th thoracic segments it became more median, lying at the apex of the posterior columns just behind the posterior commissure. In the 12th thoracic segment the hæmorrhage was much larger and passed across the mid-line in the grey commissure. It became largest, nearly 1 cm. in diameter, at the lower border of the 1st lumbar segment, and below this ran down as a central cavity in the posterior columns to the lower end of the cord (fig. 2).

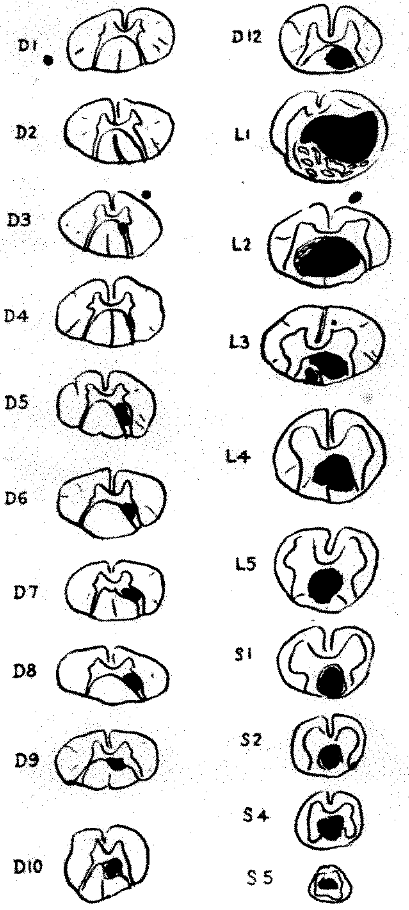

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FIG. 2.—*Case* 1. A drawing of sections of the spinal cord at various levels, showing the position of the hæmatomyelia. A central column of blood is present from Th.3 to S.5 segments. The angioma is indicated in the 1st lumbar segment. Above, the hæmorrhage is in the right posterior horns; below, it is in the posterior columns.

The physical signs coincided accurately with this distribution of the hæmorrhage. The band of sensory loss from 5th to 9th thoracic segmental levels was due to hæmorrhage in the right posterior horn. From the 9th to the 12th thoracic levels the hæmorrhage had spread out of the grey matter, and in those dermatomes sensation was preserved. At the 1st lumbar segment the massive hæmorrhage had caused a complete transverse lesion, below which motor power, sensation and reflex activity were lost.

Histological examination.—On the posterior part of the section through the area of largest hæmorrhage one could faintly distinguish macroscopically a small, oval, yellowish, porous-looking area of abnormal tissue. Microscopically, this was found to be a small angioma confined to that segment (fig. 3). It consisted of a localised collection of large and small thin-walled blood sinuses. In a few of these the structure resembled normal veins, but they mostly consisted of a thin layer of collagen, with a single lining layer of flattened epithelium. There were some localized hyaline thickenings of the walls. The tissue between these sinuses was composed of hyperplastic glial tissue infiltrated by hæmorrhage, of scattered bands of connective tissue and some nerve fibres. An actual point of rupture of one of the larger sinuses could be seen in some of the sections.

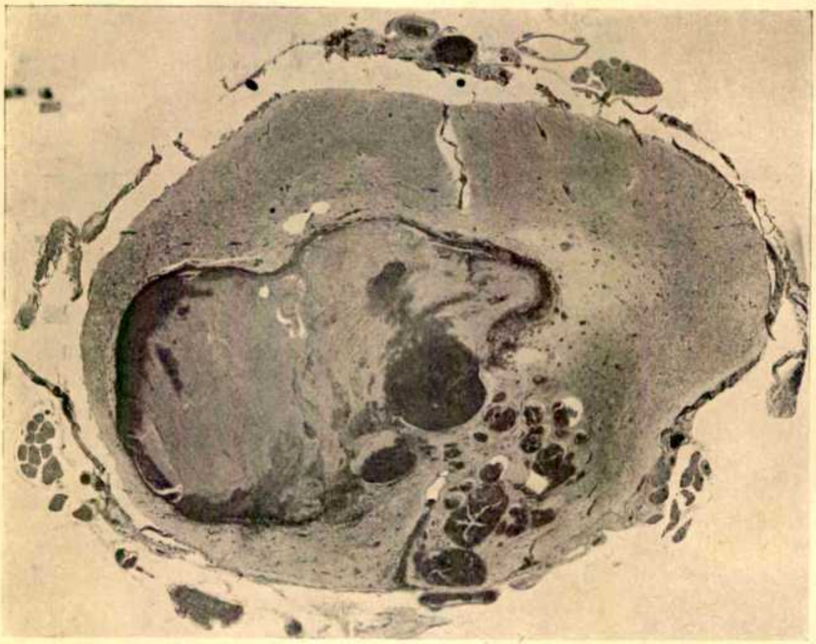

FIG. 3.—*Case* 1. Section through the angioma, showing a ruptured vessel and the adjoining large hæmorrhage. (× 6.) Hæmatoxylin and Van Gieson.

The clinical symptoms suggest that a slow leakage occurred at first, then a more massive hæmorrhage. This severe hæmorrhage following a game of football was probably provoked by the spinal venous congestion ensuing upon the strenuous exertion. Trauma was in that sense a secondary precipitating factor.

The hæmorrhage appeared recent, being composed of intact red blood-cells centrally, with a relatively small amount of blood pigment at the periphery. This pigment was greatest in amount in the 1st and 2nd sacral segments. The white matter at the margin of the hæmorrhage was severely degenerated and there was some proliferation of capillaries, and perivascular infiltration of lymphocytes. In the grey matter of both anterior and posterior horns there were pronounced degenerative changes in the nerve-cells, with well-defined neuronophagia and falling out of cells (Plate I, fig. 4).

Vascular tumours and malformations of the spinal cord are rare, but in the cases reported hæmatomyelia is not an uncommon complication. Lissowsky (1933) reports a case in a 49-year-old man, very similar to the above described, in which there had been no symptoms prior to the terminal hæmatomyelia. The vascular lesion was very similar to ours, and was almost invisible macroscopically. Also in Buckley's case (1936) of a large cervical angioma there was little or no clinical manifestation until a hæmorrhage in the grey matter extending to the lower thoracic region terminated fatally. In that angioma a more mature type of blood-vessel is described. Similar vascular lesions reported by Guillain, Schmite and Bertrand (1932), by Ohlmacher and by Bremmer and Rossolimo (quoted by Lissowsky) have very similar features and were complicated by hæmatomyelia. Russell (1932) reported a case of capillary hæmangioma of the spinal cord with extensive cavitation, which may have been the relic of a hæmatomyelia. Such "angiomata" are probably developmental vascular malformations rather than true tumours. They tend to occur in either the cervical or lumbar enlargements.

True vascular tumour, or hæmangioblastoma, may also occur in the spinal cord, though much less commonly than its favourite site in the cerebellum. (Lindau, 1930-31; Bucy, 1932). They are said to be situated in the posterior part of the cord almost exclusively (Wolf and Wilens, 1934). They may or may not be associated with the features of Lindau's disease (viz. cerebellar tumour, angioma of retina, and cysts of pancreas and kidney). Their true neoplastic nature is shown histologically by endothelial proliferation, excessive formation of reticulin fibres, and the absence of nerve fibres between the smaller vascular channels. The association of hæmatomyelia with these tumours is not as well defined as in the angiomatous malformations above described. Spinal hæmangioblastoma is often associated with cystic cavitation of the cord or with syringomyelia, which may possibly in some cases be the end result of a hæmatomyelia, as suggested by Russell. Clinically they are said to give rise to frequent exacerbations of symptoms. Detailed considerations of the pathological features of the various types of vascular maldevelopments and tumours is beyond the scope of this report. The distinction between neoplasm and maldevelopment in these lesions is somewhat difficult, and there is a good deal to suggest that hæmangioblastoma also begins as a vascular anomaly.

Case 2.—*A man, aged* 58, *who was admitted to the National Hospital under the care of the late Dr. Kinnier Wilson on September* 12, 1936, *and died on January* 1, 1937.

Clinical history.—He was well until April, 1935, seventeen months before coming to hospital. At that time he was suddenly awakened at night by severe pain across the lower abdomen. There was a rapidly increasing weakness of the legs in the next two days. Twenty-four hours after the onset he had developed a numb patch over the upper part of the front of his right thigh. After two days the legs, bladder and bowel were completely paralysed and he had a numb dead feeling up to the waist. In St. Mary's Hospital soon after the onset an examination of the cerebrospinal fluid showed a strongly positive Wassermann reaction, 15 lymphocytes per c.mm., a raised globulin content and a meningitic gold curve. The blood Wassermann was also positive and he was treated by administration of iodide, mercury and bismuth.

He remained in the same state for the first month and then gradually recovered. Bladder and bowel functions returned to normal in the second month. Power returned more slowly in the legs and he suffered a constant, tight, painful sensation in the legs and about the hips, with painful flexor spasms of the legs. He was able to walk with crutches five months after the onset. One year after the onset of symptoms he began to have much more severe pain in the legs and this brought him to hospital.

Clinical examination.—He looked old, thin, weak, and tortured by continued pain. The pupils reacted a little sluggishly to light, otherwise the cranial nerves were normal. The arms and trunk were normal. There was a severe spastic paraplegia, the right leg somewhat more rigid and weak than the left. There was some local wasting of the glutei, hamstrings and quadriceps. No definite sensory level could be determined on repeated careful examination. Appreciation of light touch was slightly impaired over both feet and legs below the knees. The sense of position and passive movement was grossly impaired in the right foot and decreased on the left. Vibration sense was lost in both legs. The knee and ankle jerks were exaggerated with a right ankle clonus and bilateral extensor plantar responses.

Examination of the other systems was negative except for fairly pronounced arteriosclerosis in the retina and peripheral vessels.

The cerebrospinal fluid was now normal and the Wassermann reaction was negative in the cerebrospinal fluid and blood.

Summary.—This was a 58-year-old syphilitic male who, seventeen months previously, had a sudden onset of severe abdominal pain and complete paralysis of legs, bladder and bowel. He recovered progressively for several months but marked weakness and rigidity of the legs remained. One year after the onset he began to have more severe pain in the legs. There was no sensory level but the muscular wasting suggested a lesion as high as the 2nd lumbar segment, and the early history suggested a lesion as high as the 10th or 11th thoracic segments.

Dr. Wilson's clinical diagnosis was syphilitic "thrombomyelia," an apt term of his own invention designating thrombotic softening of the spinal cord.

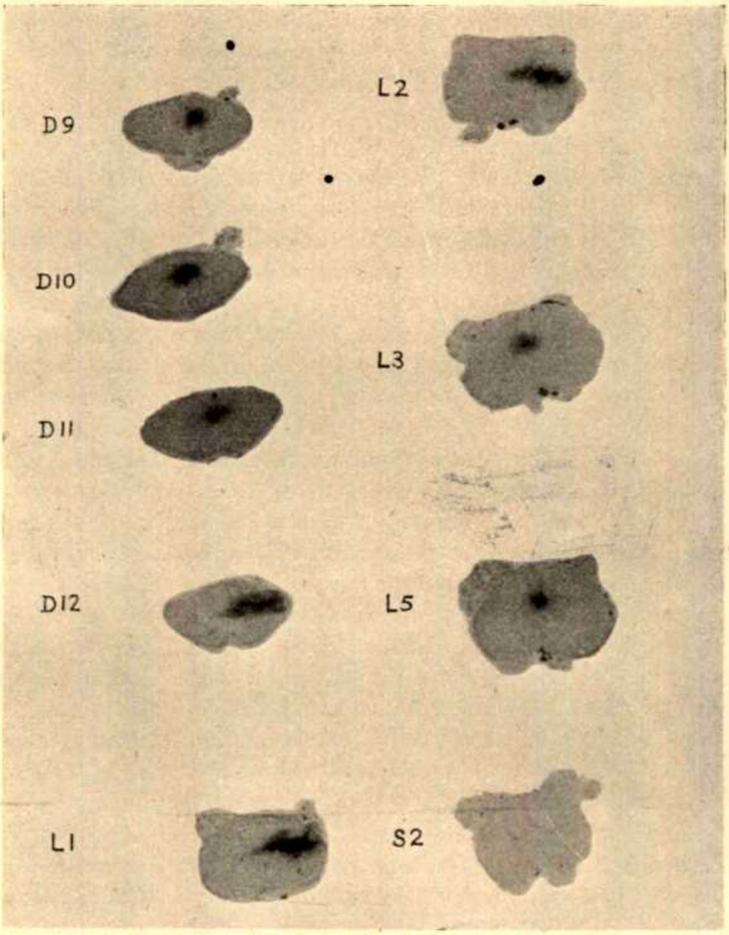

FIG. 5.—*Case* 2. Sections of the spinal cord in thoracic and lumbar segments, stained for iron to show the position of the old hæmorrhage. (× 2·3.)

In hospital the patient became progressively worse from an intervening infection of the bladder and bowel which led to his death twenty months after the onset of symptoms.

Post-mortem examination.—Examination of the spinal cord showed slight thickening and sticky adhesions of the leptomeninges over the dorsal surface. Some softening could be felt in the region of the 12th thoracic segment.

Sections of the cord showed the brown scar of an old hæmatomyelia extending from the 9th thoracic to the 4th lumbar segments. The pigmented area stained deeply by the Prussian blue reaction for iron (fig. 5). Above, the area of old hæmorrhage was small and rounded, lying just behind the posterior commissure. It became larger as it was traced downwards and showed a lateral extension to the right and lateral margin of the cord in the 12th thoracic and 1st and 2nd lumbar segments, thus involving the posterior column, base of posterior horn, and lateral column. At the 1st lumbar segment it also involved the base of the anterior horn. In the 3rd and 4th lumbar segments the hæmorrhage was again small and tubular, and confined to the right posterior column.

Histological Examination.—Microscopically, there was no cavity, nor were there any free red blood-cells. There was a heavy deposit of old brownish blood-pigment, mostly contained in macrophages forming thick cuffs around the vessels in the posterior columns (Plate I, fig. 6). Several lymphocytes were scattered amongst the pigment-laden phagocytes. In some areas the vessels were surrounded by a pure round-cell infiltration. In other places the whole thickness of the vessel was infiltrated by lymphocytes, sometimes causing a slight inward bulging of the intima. A localized inflammatory reaction of this type was well defined in one large pial vein. This reaction, occurring distinct from the perivascular cuffing by macrophages containing iron pigment, was the most definite evidence of syphilitic vascular disease that was found. The exact source of hæmorrhage was not detected, but it seems possible that rupture occurred in one of these small syphilitic (?) vessels.

A dense glial scar was present in the area of pigmentation, most pronounced centrally, with a lateral projection through the posterior horn to the lateral column in some areas. Large astrocytes with heavy neuroglial fibres were seen by phosphotungstic acid hæmatoxylin staining. There was also a pronounced marginal gliosis, with tufts spreading into a thickened pia.

Pronounced local destruction of myelin and nerve fibres was shown by Loyez stain as pale areas in the area of pigmentation and scarring (Plate I, fig. 7). There was also a well-defined ascending degeneration in the posterior columns and descending degeneration in the pyramidal tracts (Plate I, fig. 8).

This long, tubular and flattened strip of blood pigment is probably the relic of an extensive hæmorrhage. Its distribution is similar to that of the first case, though probably the hæmorrhage was smaller. The history of rapid onset with pain supports clinically the contention that the lesion was hæmorrhagic. The hæmorrhage cavity had been entirely filled by a glial scar, and the resulting picture was one of old hæmorrhage rather than of softening,

There have been a few reports of syphilis as a cause of hæmatomyelia, though it would seem distinctly uncommon. In the case report of Roger, Antonin and Poinso (1928), entitled "Syphilitic Softening of the Cord," the pathological findings were very similar to the case here reported.

R. T. Williamson (1911) recorded another case of syphilitic hæmatomyelia. Chung (1926) reports thirty-four cases of syphilitic paraplegia of rapid onset. Though thrombosis was probably the cause in most of these cases, some may well have been due to hæmorrhagic lesions. Chevallier and Desoille (1930) consider hereditary syphilitic vascular lesions as the most important cause of vascular weakness in spontaneous hæmatomyelia, though their report contains no convincing proof of that opinion. In Brooks' report (1916) of four cases of hæmatomyelia, two were syphilitic.

Case 3.—*Spontaneous Cervical Hæmatomyelia.*

This was a 31-year-old man seen in consultation at a L.C.C. Hospital by Dr. Purdon Martin. I am grateful to him for the following clinical notes.

Clinical history.—The patient was well until three weeks before his death.

His illness began suddenly with severe pain in his neck radiating to both shoulder blades. Severe pain persisted and the following day he gradually lost the use of his left arm. Micturition was difficult from the onset, passing to complete retention just before his admission to hospital on the twelfth day of the condition. His left leg had been a little weak for a few days before coming into hospital.

Clinical examination.—The left pupil was slightly constricted, otherwise the cranial nerves were normal. There was a flaccid paralysis of the left arm with absent reflexes. Power was good in the right arm, but all tendon reflexes were sluggish. Power was moderately impaired throughout the left leg, with slight rigidity, increased knee and ankle jerks, and an extensor plantar response. In the right leg power was normal, knee and ankle jerks normal, and plantar response doubtfully extensor. Sensation to pin-prick and cotton-wool was impaired over the 6th and 7th cervical dermatomes on the left. There was a moderate impairment of sensation to pin-prick over the whole right side of the body below the 4th cervical distribution. The cerebrospinal fluid was normal; the protein estimation was 0·025 per cent.; there was no evidence of block; and the Wassermann reaction was negative in the cerebrospinal fluid and blood.

The signs thus clearly indicated an intramedullary lesion of the cervical enlargement extending up to the 4th cervical segment, and producing a Brown-Séquard syndrome. The diagnosis was considered to rest between some form of acute myelitis and a vascular lesion, probably the former.

Full notes of his progress are not available. He remained acutely ill and on October 1 became unconscious. On that day he passed a blood clot from the bladder. There was thought to be a slight right facial weakness. He died later on the same day three weeks after the onset of symptoms.

Post-mortem examination.—Nothing grossly abnormal was detected in other organs than the brain and spinal cord. The brain was generally congested but showed no petechial hæmorrhages or other focal macroscopic lesions. Examination of the spinal cord at autopsy showed an irregularly rounded hæmorrhage into the left side of the cord from the 3rd to the 7th cervical segments. The hæmorrhage was mostly in the grey matter involving both anterior and posterior horns. Above, it extended also into the left lateral column.

A portion of the cervical spinal cord was received for examination at the National Hospital pathological laboratory. The cord had been severely damaged in removal, so that the naked-eye picture could not be satisfactorily studied in the fixed material, and only part of the mid-cervical cord was sufficiently intact for section cutting. In the sections made from the 6th cervical segment there was a well-defined transversely-lying oval area of hæmorrhage in the left lateral column (fig. 9). The anterior and posterior horn cells on that side showed moderately severe degenerative changes, namely, central chromatolysis with poorly staining eccentric nuclei. The neighbouring blood-vessels in the cord were congested, but no vascular disease or anomaly was demonstrable. There was no evidence of any acute inflammatory process.

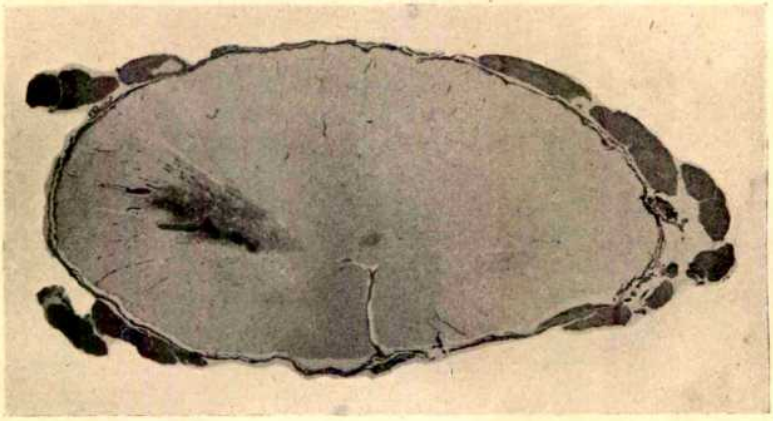

FIG. 9.—*Case* 3. Recent hæmorrhage in the left posterior horn and lateral column (× 5.) Hæmatoxylin and Van Gieson.

The investigation in this case was necessarily incomplete. It serves merely to illustrate the clinical features of hæmatomyelia, with a rough picture of the pathology. Though no vascular weakness was demonstrated, it is quite possible that a source and a cause of the hæmorrhage were missed.

Case 4.—*Cervical hæmatomyelia. Survival with residual weakness.*

A man, aged 38, *who was in the National Hospital under the care of Dr. Hinds Howell.*

Clinical history.—This patient, a painter, was well until September 18, 1935. On that morning, while at work, he felt a sudden pain in both arms from shoulder to finger tips, which continued, and was followed six hours later by a noticeable weakness and clumsiness of his fingers. In the subsequent few hours the weakness in his hands increased to almost total paralysis. On awakening the next morning his hands and fingers were powerless, and he was unable to move his right leg; the pain had then entirely disappeared. Power seemed good in his elbows, shoulders and in his left leg. He was too weak to sit up in bed. His hands at this time felt numbed and senseless. There was a numb, cold sensation over the right foot and leg up to the lower thigh, which spread up over the right thigh and the right half of the abdomen in the following hour. Also, on the second day, he had complete retention of urine, though he could feel his bladder distended.

He was taken to Fulham Hospital on the third day of his illness. There, the bladder function gradually recovered, but his condition remained otherwise unchanged for two or three weeks.

About three weeks after the onset, power began to return in the right leg and the left arm. They improved rapidly for a fortnight and then more gradually up to the time of coming to hospital. The numb sensation of the right leg and lower trunk passed off entirely in the first few weeks. The right hand showed no recovery for three or four months, and remained much weaker than the left. Wasting was noticed in his hands a few months after the onset.

About four months after the beginning of his trouble he noticed, when taking a hot bath, that he could not appreciate heat with his left leg. This sensory disturbance remained unaltered from that time.

Clinical examination.—The cranial nerves were normal except for a slight left ptosis. Motor functions were normal in the neck and shoulder girdle.

Arms: There was wasting along the front of the right forearm, particularly on the ulnar side, and marked wasting of all the small muscles of the right hand. On the left there was wasting of the first dorsal interosseous muscle only. There was marked weakness in flexion of the right fingers and wrist, power being fairly good in extension. There was no weakness of movements at the shoulder and elbow. Power was good in the left upper limb except for slight weakness in flexion and adduction of the thumb. There was no inco-ordination or fibrillation of the arm muscles, and rapidly alternating movements were performed well.

Trunk: Movement of the right side of the chest was considerably diminished, and the intercostal muscles below the third were felt to be powerless. There was some weakness of the right abdominal muscles, and the umbilicus deviated to the left.

Legs: There was no wasting of the leg musculature. Slight rigidity was noted throughout the right; the tone was normal in the left leg. Flexion of the right hip and dorsiflexion of the right foot were weak; other movements were of normal power, with no weakness on the left.

Sensation: There was a moderate hypoalgesia to pin-prick over the trunk on both sides from the 2nd to the 10th thoracic segments, and over the ulnar border of the right arm. Appreciation of heat sensation was slightly impaired over the left lower abdomen and over the outer part of the left leg.

Reflexes	*Right*	*Left*
Biceps-jerk	Normal	Weak
Triceps-jerk	Normal	Weak
Supinator-jerk	Normal	Weak
Finger-jerk	Absent	Weak
Abdominal	Weak	Normal
Knee-jerk	Brisk	Normal
Ankle-jerk	Normal	Weak
Plantar reactions	Extensor	Flexor
Ankle clonus	None	None

His gait was marked by dragging of the right foot.

Summary.—A 38-year-old man who experienced a sudden onset of pain in the arms and then weakness of the hands. This was followed the next day by total paralysis of the hands, right leg and bladder, weakness of the trunk muscles, and subjective sensory loss over the right leg and right side of the trunk. Recovery occurred gradually with residual weakness and wasting of the upper limbs and a spastic weakness of the right leg. Loss of heat sensation was noticed in the left leg some time after the onset.

Examination fourteen months after the onset showed weakness and wasting of the flexor muscles of the right hand and wrist and of the mucles of the left thumb, with weakness of the right intercostal and abdominal muscles. The right leg was slightly rigid and weak. Sensation to pin-prick was impaired from the 2nd to the 12th thoracic segmental areas bilaterally and heat appreciation was diminished over the left leg and lower abdomen (Th. 10 and 11 and L.5).

Diagnosis.—The lesion in this case can be accurately localised as an elongated, central lesion in the cord, involving the anterior horns in the lower end of the cervical enlargement, spreading down in the posterior commissure and posterior columns, causing a dissociated sensory loss over both sides of the trunk and loss of deep sensation in the legs. It apparently extended out into the right lateral column at some point to cause the ipsilateral pyramidal tract signs and the partial contralateral sensory loss due to encroachment on the spinothalamic tract.

The involvement is so well localized to the central part of the cord as to make a diagnosis of myelitis unlikely. The picture is rather like that of syringomyelia. The sudden onset in a previously healthy man makes one fairly confident of a diagnosis of haematomyelia with persistent cavitation and gliosis of the cord.

It seems reasonable that some local vascular weakness was present, probably in the cervical enlargement, to account for this apparently spontaneous hæmorrhage. In the absence of signs of arteriosclerosis and of syphilis or other infection, an intramedullary tumour, or vascular maldevelopment, such as in Case 1, are possibilities.

(3) DISCUSSION.

(i) *Symptomatology.*

The onset of spontaneous hæmatomyelia is characteristically sudden, as these cases all illustrate. In Case 1 the prodromal symptoms of spreading numbness and then weakness of one leg, preceded the rapid onset of a complete paraplegia. In Case 2 and 4 the symptoms reached their maximum only after twenty-four and forty-eight hours. Many reported cases have had a much more rapid onset, a complete powerlessness of the legs supervening within a few hours or even minutes. In fact Gowers and others doubted the possibility of prodromal symptoms in primary hæmatomyelia, and suspected that all such cases were myelitic in origin.

Though symptoms vary with the site of the lesion, there is usually a total paraplegia of the legs, a definite sensory level below which all forms of sensation are lost, and paralysis of the bladder and bowel.

Pain is said to be common but not invariable. It was a symptom common to all four of the cases here reported, and was a striking feature in the first two cases. The pain is probably of central origin due to hæmorrhage into the posterior horns. It seems unlikely that swelling of the cord, sufficient to compress the nerve roots, would occur. In all cases the initial pain in the affected limbs disappeared with the arrival of complete paralysis. In Case 1 there was also severe pain in the back which persisted throughout the illness. In the syphilitic case the occurrence of severe pain in the legs, a year after the onset, suggests a relation to the forming of a glial scar in the posterior horns. In Case 4 the minimal occurrence of pain corresponds with the suggested location of the hæmorrhage, in that it did not apparently affect the posterior horns to any great extent.

Tenderness over the vertebral spines, as was noted in one of these four cases, has been frequently described in the older writings on hæmatomyelia.

The *prognosis* in primary hæmatomyelia is difficult in view of the several different possibilities for the course of the disease. In severe cases death may occur in a few hours or days, and Doerr mentions two cases of sudden death. The rapidly fatal cases are chiefly those of hæmorrhage into the cervical cord. In other cases a fatal outcome may result after a few days or weeks, in which the course is almost always secondary infection of the urinary tract, or decubitus. The three fatal cases here reported tall into this group, though in the second case a terminal infection occurred as a much later event. Though exact figures are not available, it appears that a large proportion of the cases are less severe and do not terminate fatally. It is in some measure characteristic of hæmatomyelia that the symptoms, after reaching a maximum, often with an initial picture of spinal shock, subside to a considerable degree. Gradual recovery occurs over a period of several months as in our fourth case, leaving permanent more or less severe paralyses and sensory loss.

It is conceivable that a long, central hæmorrhage in the spinal cord may eventually result in a pathological and clinical picture very like syringomyelia. Minor suggested from such observations the "hæmatomyelogenous" theory of development of syringomyelia. Krause and Glatt (1934) and others have reported clinical observations corroborating the conception of central cavitation of the cord beginning as a hæmorrhage. D. S. Russell's report of angioma with cavitation and gliosis is a case in point. The fourth case here reported also had a final clinical picture not unlike syringomyelia. Though central cavitation and gliosis may undoubtedly be produced, the picture of true syringomyelia or syringobulbia has its own distinct features and has not been reproduced by old hæmorrhage.

In this discussion of the symptoms and course of the diseases, the articles and reviews of Gowers, Oppenheim, Batten, Lépine, Minor and Doerr have been consulted. The reader is referred to those works for more detailed descriptions of clinical features, differential diagnosis and treatment.

(ii) *Ætiology.*

As previously mentioned, it is generally stated in the literature that trauma is much the commonest cause of hæmatomyelia, but if one considers this in the usual sense of a large, central hæmorrhage spreading longitudinally, it seems probable that the importance of this factor has been exaggerated. Some of the early case reports have been merely clinical without post-mortem confirmation. In other cases of direct injury to the cord, a localized pulping, softening and hæmorrhage has been termed hæmatomyelia (Ballance, 1897; Thorburn, 1889). The diagnosis of hæmatomyelia is often based on clinical findings suggestive of spinal cord damage over several segments, the assumption being that a central hæmorrhage has occurred.

Holmes (1915), in his study of spinal injuries of warfare, was impressed by the fact that hæmorrhages were by no means the outstanding pathological feature of direct injury to the spinal cord. A true hæmatomyelia, defined as above, was not found in any of his fifteen cases. "Hæmorrhages, generally small, but occasionally of considerable size, are usually found in these softened areas" (at the site of injury), "but they are more common and as a rule larger in grey, than in white matter. In many cases, however, hæmorrhages have been few or very small and they are evidently not a feature of the condition." The distant lesions which he found over several segments on each side of the local pulping of the cord, and which seemed of much more significance than hæmorrhage, were œdema and softening, localized swelling of axones, degeneration of nerve-cells, patches of necrosis and vacuolation, and peculiar cylindrical non-hæmorrhagic cavities. Similarly in contusion and concussion, hæmorrhages were minute and scattered, and the striking features were œdema, softening, focal necrosis, and vacuolation of white matter.

Jefferson (1936), more recently, has expressed the same opinion, minimizing the importance of hæmatomyelia in spinal cord injuries. He states that though local hæmorrhage is present at the site of a direct injury to the cord, it is not a feature of those cases of fatal contusion of the cervical cord in which the only gross lesion is a diffuse swelling. To quote from his article concerning spinal contusion: "It is doubtful whether such a state as 'hæmatomyelia' actually exists. It is more probable that the clinical syndrome which we call, and no doubt shall continue to call, 'hæmatomyelia,' is due to a local neural disruption, to relatively bloodless contusion, rather than to intramedullary clot."

Granted that hæmorrhage may occur over several segments in a few cases of spinal cord injury, and may well be most marked in the gray matter, it is then usually associated with marked softening, and is a hæmorrhagic softening, rather than a pure, central blood-clot.

The high incidence of traumatic hæmatomyelia in the literature if further increased by terming "traumatic," cases in which the precipitating factor of a hæmatomyelia was excessive exertion or mild direct injury (Zwirn, 1928; Fox, 1876; Sharkey, 1891). Oppenheim (1911) remarked on the difficulty in judging the importance of trauma in such cases, and Doerr pointed out that there was probably some underlying weakness of spinal blood-vessels. It seems likely that most of such cases belong in the group "spontaneous hæmatomyelia." Thus, in our first case in which there was an intramedullary angioma, the actual hæmorrhage was precipitated by the exertion of playing a game of football.

The term, "spontaneous hæmatomyelia," is best understood as meaning a primary, non-traumatic, elongated, central hæmorrhage of the cord, occurring in the absence of preceding symptoms of a spinal cord lesion. It is difficult to conceive such a hæmorrhage occurring from healthy vessels, and the writer takes the view previously emphasized by H. Brooks (1916), that there is always some fault in the vessels. (In the latter's four cases the hæmorrhages were ascribed to syphilis and arteriosclerosis with an added factor of alcoholism.) In this sense such hæmorrhages are really secondary, but the term "secondary hæmatomyelia" would be better reserved for those cases occurring with spinal cord tumour, syringomyelia and myelitis, which had in themselves previously produced spinal symptoms. Thus, in the first two cases here reported, the term spontaneous hæmatomyelia is applicable. Though the hæmorrhage was caused by a minute angioma, and by syphilitic vascular disease, the hæmorrhage was the first clinical manifestation of spinal disease.

A useful analogy can be drawn with the intracranial condition of spontaneous subarachnoid hæmorrhage. In that syndrome there is always some vascular disease and we now recognise "berry" aneurysms of the circle of Willis to be much the commonest form of this. In the much rarer condition of spontaneous hæmatomyelia, observations are too few and incomplete for any comparable certainty of our knowledge of ætiology. Intramedullary vascular tumours and malformations may eventually prove the commonest causes, with syphilis, acute myelitis and arteriosclerosis contributing a smaller share.

(iii) *Summary.*

Four cases of the rare condition "spontaneous hæmatomyelia" have been presented. The first and second of these exemplify two of the causes of the condition.

In the first case there was a small angioma in the 1st lumbar segment of the spinal cord which had ruptured, causing a central hæmorrhage from the 4th thoracic to the lowest sacral segment. The "angioma" was considered a developmental vascular lesion rather than a tumour. Previously reported cases having a similar cause have been cited.

The second case was one of old hæmatomyelia occurring with syphilitic meningomyelitis. A central hæmorrhage has occurred from the 9th thoracic to the 5th lumbar segment, leaving an elongated strip of gliosis containing a large amount of old blood pigment.

The third case was one of cervical hæmatomyelia in which the exact cause was not demonstrable, since pathological examination was incomplete. In the fourth case hæmatomyelia was not fatal, but left permanent sensory and motor changes resembling those of syringomyelia.

The clinical features and causes of spontaneous hæmatomyelia have been reviewed with reference to these cases.

Traumatic hæmatomyelia has assumed a false position of importance in the incidence of true hæmatomyelia. Hæmorrhage is often overstressed in the conception of the pathology of spinal cord injuries.

Spontaneous hæmatomyelia should be considered as primary, non-traumatic hæmatomyelia, and is probably always due to disease or maldevelopment of the spinal vessels. Vascular maldevelopments, similar to that found in Case 1, comprise one of the commonest known causes of the condition.

These cases were studied clinically and pathologically at the National Hospital, Queen Square, during the tenure of a resident staff appointment. I am very grateful to Dr. J. G. Greenfield for the photomicrographs and for his great assistance in the pathological examinations. My thanks are also due to the above-mentioned Honorary Physicians for permission to publish the cases.

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LEGENDS FOR PLATE

FIG. 4.—*Case* 1. Anterior horn cells in the eleventh dorsal segment showing degenerative changes caused by the neighbouring hæmatomyelia. Neuronophagia is well marked. (× 400.) Nissl stain.

FIG. 6.—*Case* 2. Masses of old blood pigment forming cuffs around the vessels in the posterior columns. (× 100.) Prussian blue reaction.

FIG. 7.—*Case* 2. Twelfth dorsal segment. Pale area of myelin destruction in the region of old hæmorrhage, involving the right posterior column, posterior horn and lateral column. The meninges are somewhat thickened. (× 7·6.) Loyez stain.

FIG. 8.—*Case* 2. Second lumbar segment. Local myelin destruction and descending pyramidal tract degeneration. (× 7·6.) Loyez stain.

PLATE I.

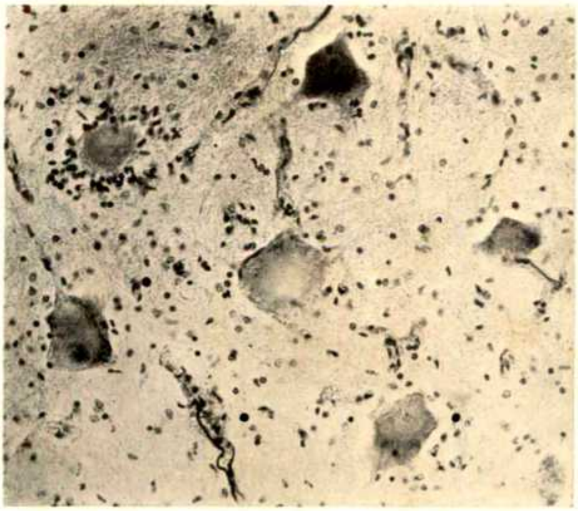

FIG. 4.

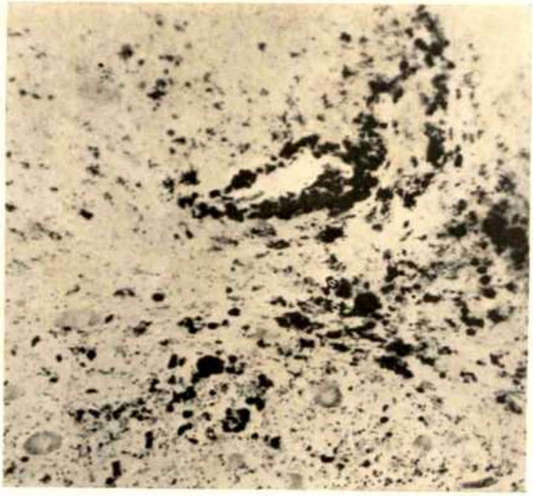

FIG. 6.

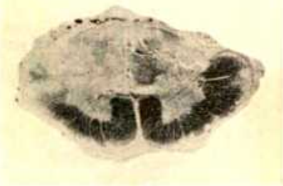

FIG. 7.

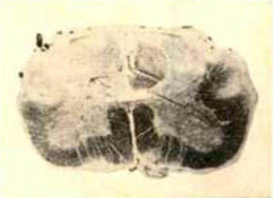

FIG. 8.

To illustrate article by J. Clifford Richardson.

ON NORMAL DISCS IN PATIENTS WITH CHIASMAL LESIONS.[1]

BY ADAMS A. McCONNELL AND ALAN J. MOONEY.

In the majority of cases of pituitary tumour the optic discs are pale, but in a certain number of cases the discs are normal in appearance or "within normal limits."

When the existence of a tumour in the neighbourhood of the chiasma has been finally established and the early case notes are reviewed in retrospect, doubt has sometimes been cast on the observation that the discs were normal in appearance. There is a widespread notion that in patients with the gross field defects that are found in such cases the discs must have been atrophic in appearance and some surgeons have been inclined to question the accuracy of the ophthalmologist's observation. This series of case reports is an attempt to show that his considered judgment may be a valuable element in diagnosis.

The paper is based on six cases of tumour involving the chiasma in which the discs were normal.

Case 1.—*K. F., male, aged* 38. *Headache, vomiting and defective vision. Bitemporal hemianopsia. Discs normal. Gross enlargement of pituitary fossa. Operation, retrochiasmal pituitary adenoma. Death. Post-mortem examination.*

The patient was admitted to the Richmond Hospital, Dublin, under the care of Dr. H. Lee Parker, on May 22, 1936.

About Christmas, 1935, his vision became blurred, printed words being indistinct and "all mixed up." Some time later objects also became indistinct.

In March, 1936, he began to suffer from headaches of a dull aching type with acute exacerbations. The acute pain was felt usually in the frontal and occipital regions, but occasionally "seemed to come out through my ears."

In April, 1936, vomiting started. It was provoked particularly by any sudden movement and occurred frequently.

Examination.—General medical and neurological examinations were negative. Ophthalmological examination showed: Right eye, corneal nebula. Vision corrected $\frac{6}{12}$, J 2. Left eye, small foreign body in the cornea. Slight hypermetropia. Vision corrected $\frac{6}{24}$, J 3. Fundi normal. Ocular movements and pupillary reactions normal. Visual fields showed complete bitemporal hemianopsia with sparing of the macula in the right eye. Basal metabolic rate −24. Glucose tolerance curve normal. Wassermann reaction negative. Radiographic examination by T. G. Hardman revealed an extremely large sella turcica with almost complete destruction of the dorsum sellae.

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[1] From the Neurological Department of the Richmond Hospital, Dublin.

June 27, 1936: Transfrontal exposure of chiasmal region. The right optic nerve passed straight backwards from the optic foramen. It appeared normal. At first sight the pituitary fossa appeared empty, but when the nerve was traced backwards a tumour appeared in the middle line below the chiasma. A needle was passed into it and some old blood was aspirated. An incision opened a firm-walled cavity containing a considerable amount of dark blood. With a curette and with pituitary rongeur forceps, a small amount of tissue which seemed to line the wall of the cavity was removed and part of the wall was excised. The condition seemed to be that of a hæmorrhagic cyst in a pituitary tumour and it was hoped that the evacuation of the cyst would be sufficient to relieve the patient's symptoms. The wound was closed. The patient seemed to be recovering satisfactorily, but forty-eight hours after the operation he became comatose and died.

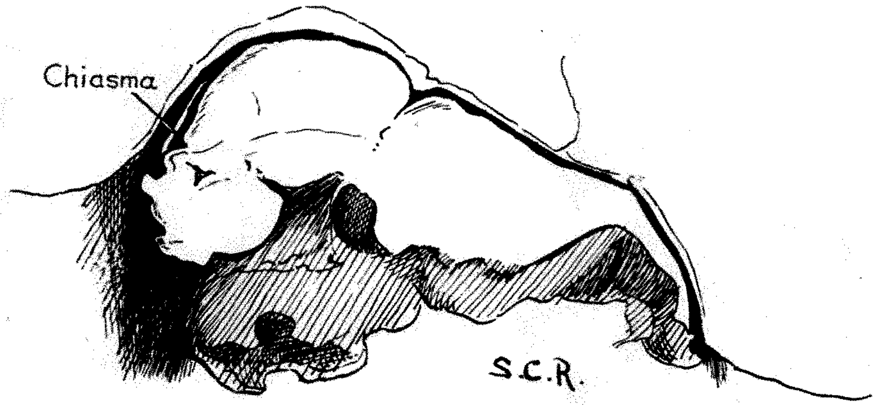


FIG. 1.

Post-mortem examination revealed a large pituitary tumour filling most of the 3rd ventricle and extending backwards to the pons. The optic chiasma was reduced to a thin membrane as it stretched across the front of the tumour (fig. 1). Below the chiasma were the remnants of the cyst which had been evacuated at the operation. Even when distended with blood it did not seem probable that the cystic portion would have pressed on the optic nerves. The optic nerves seemed to emerge abruptly from the anterior surface of the flattened chiasma; they were not flattened. On the upper aspect of each nerve at its junction with the chiasma was a deep groove caused by the anterior cerebral artery.

Microscopic diagnosis: chromophobe adenoma.

Case 2.—*D. O., male, aged* 40 *years. Headache and vomiting for five months. Nearly blind. Discs normal. Pituitary insufficiency. Operation, retrochiasmal tumour. Recovery of vision. Left homonymous hemianopsia.*

The patient was referred to the Richmond Hospital, Dublin, on July 12, 1937, by Mr. Deane, of Belfast, on account of blindness.

About the middle of March, 1937, he noticed that "words ran into each other," and later that his vision was "misty." Occasionally he had diplopia.

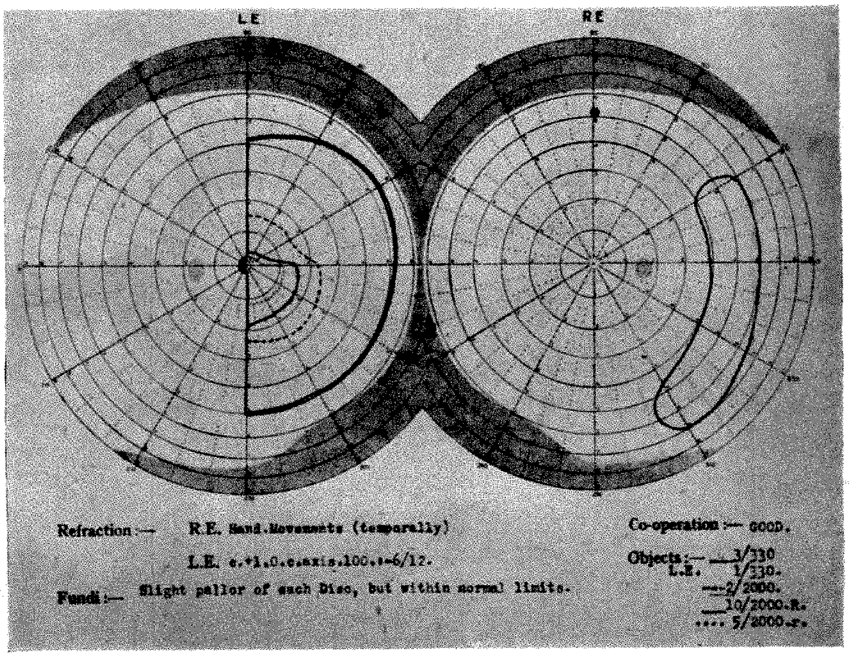

L.E.
R.E.
Refraction :— R.E. Hand.Movements (temporally)
L.E. c.+1.0.c.axis.100.:-6/12.
Fundi :— Slight pallor of each Disc, but within normal limits.
Co-operation :— GOOD.
Objects :— 3/330
L.E. 1/330.
2/2000.
10/2000.R.
5/2000.r.

Fig. 2.

A diagnosis of nicotine poisoning was made, but appropriate treatment for that condition had no effect.

In April he began to suffer from headaches, which were very severe at their onset. He had one attack of vomiting after a meal and frequent attacks of nausea.

He had been putting on weight for the past two years and "had not to shave as often as formerly."

Examination.—Fat, flabby and pale in appearance. The chin looked as if he had never shaved and was sparsely furnished with hair. He was intelligent and co-operative. No abnormal neurological findings.

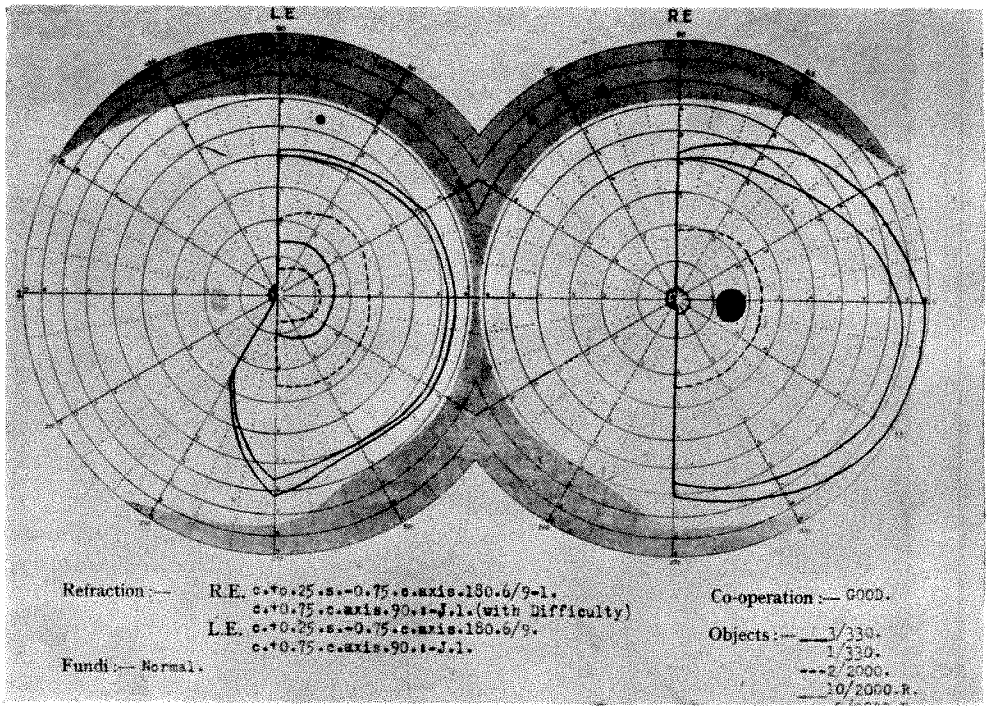
July 14, ophthalmological examination. Right eye, no perception of light, pupil inactive. Left eye, perception of light in nasal field and pupil reacts to stimulation of temporal side of retina. Discs normal, arteries small, veins slightly congested.

The floor of the sella turcica and the dorsum sellæ were eroded.

July 18, ventriculography showed that the outline of the 3rd ventricle was transverse rather than vertical, and this suggested the presence of a large tumour encroaching on the ventricle from below.

Operation, right transfrontal exposure of the chiasmal region.

The dura was opened and the anterior part of the falx resected. The mesial aspects of the frontal lobes were adherent behind the free edge of the falx. Elevation of the right frontal lobe exposed the right optic nerve, which was normal in its appearance and course. The chiasma was exposed, apparently pushed forward by the tumour which appeared below and somewhat in front of it. A needle was passed into the growth and some yellowish fluid withdrawn. It was not oily. An incision allowed a large quantity of this cystic fluid to escape, and the cyst wall collapsed. A portion of the wall was removed and the wound closed.



Refraction :— R.E. c.+0.25.s.-0.75.c.axis.180.6/9-1.
c.+0.75.c.axis.90.:-J.1.(with Difficulty)
L.E. c.+0.25.s.-0.75.c.axis.180.6/9.
c.+0.75.c.axis.90.:-J.1.

Fundi :— Normal.

Co-operation :— GOOD.

Objects :— ___3/330.
1/330.
---2/2000.
___10/2000.R.

Fig. 3.

The patient was very irritable and disoriented for several days after the operation, but on the sixth day he became rational and said that he could see. On the tenth day he was reading the newspaper comfortably.

Perimetry on August 8, 1937, showed a left homonymous hemianopsia (fig. 2), and further improvement was shown in the charts made on September 15 and November 7 (fig. 3).

Microscopic finding: Chromophobe adenoma.

Case 3.—H. D., male, aged 34. Spontaneous subarachnoid hæmorrhage. Headache and failing vision. Bilateral central scotoma. Normal discs. Operation, subchiasmal aneurysm opened and packed with muscle. Complete relief of headache and disappearance of scotomata.

The patient was admitted to the Richmond Hospital, Dublin, August 11, 1936.

History.—The patient had been in perfect health until May 16, 1936. On that day at 7.30 p.m. he was brushing his clothes when he cried out suddenly and fell to the ground unconscious. He vomited several times before the ambulance arrived. On admission to the Meath Hospital at 8.55 p.m. he was unconscious. The right side of the body was in a state of flaccid paralysis and the left in a state of spasm. He was grinding his teeth and had bitten his tongue. The pupils reacted to light. About an hour after admission he became very restless and his left arm and leg had to be held forcibly. He was incontinent of fæces. A quarter grain of morphia made him quiet and he slept. There was a small lacerated wound over the right eye. Next day the right hemiplegia was less marked and he rapidly regained power in his limbs. For two days he was extremely restless except when under the influence of morphia. He talked incoherently and vomited everything that was given to him.

May 19 he was quieter and apparently more conscious of his surroundings. Vomiting continued.

May 20: Dr. H. Lee Parker saw him and made the following note: "No clear evidence of illness prior to recent episode. At present complaining of headache; is somewhat drowsy and stupid and remembers nothing prior to Saturday, May 16, at 2 p.m. He converses rationally and has no speech defect. Examination shows suggestive œdema of both optic discs, but it is not definite. Weakness right side of face and slowness in the movements of the right arm and leg. Tendon reflexes more active on *left* side. Plantar response flexor both sides. Neck rigid. Kernig positive."

He suggested the possibility of rupture of a congenital aneurysm of the circle of Willis and recommended lumbar puncture. The cerebrospinal fluid contained much blood. The Wassermann reaction was negative.

From this date the patient made a rapid recovery except for the persistence of a dull wandering headache. He left hospital apparently well on June 25, 1936.

On July 22 he got a sensation as of something spinning in his head, and he fell. He could hear, but could not move his limbs. The attack lasted but a few minutes. After this attack the headache returned, and became so severe that he was admitted to the Richmond Hospital on August 11, 1936.

Examination.—Blood-pressure systolic 95 mm., Hg, diastolic, 60. There were no neurological signs or symptoms with the exception of nystagmus on extreme lateral deviation of the eyes. The optic discs were normal and the visual fields full. R.V. corrected, $\frac{6}{18}$. L.V. corrected, $\frac{6}{12}$. The defective vision recorded was probably due to the fairly high refractive error, the patient not having worn glasses previous to his admission to hospital. The cerebrospinal fluid showed no increase in the number of cells or in the amount of protein. Pressure 120 mm. of water. Radiographic examination of the skull showed no abnormality, while that of the chest revealed considerable fibrosis but no active pulmonary disease.

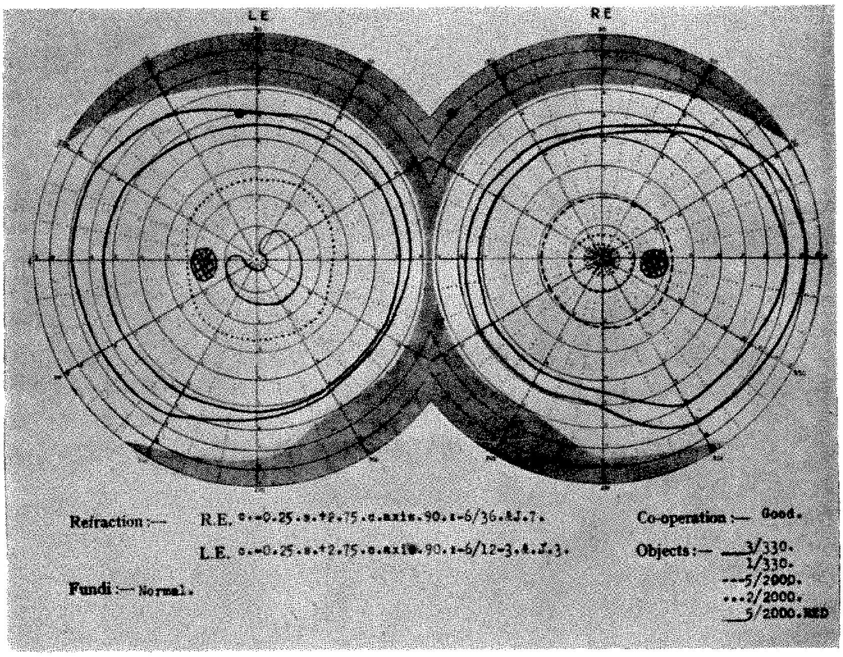


FIG. 4.

September 25: Encephalography. Nothing abnormal was disclosed. Exacerbation of headache. Headache continued and became worse until October 30, when the patient complained of blurring of vision.

November 1: Vision, right eye $\frac{6}{36}$; left eye $\frac{6}{12}$. Perimetry revealed a central scotoma in each eye (fig. 4). That in the left for red objects only.

The flaccid paralysis of the right side of the body immediately after the initial attack of subarachnoid hæmorrhage suggested a sudden anæmia of the left side of the brain probably due to rupture of an aneurysm of the left common carotid artery. There was no satisfactory explanation of the bilateral central scotoma. Bitemporal defects, both scotomatous and non-scotomatous, have been described in cases of aneurysm of the circle of Willis, but we found

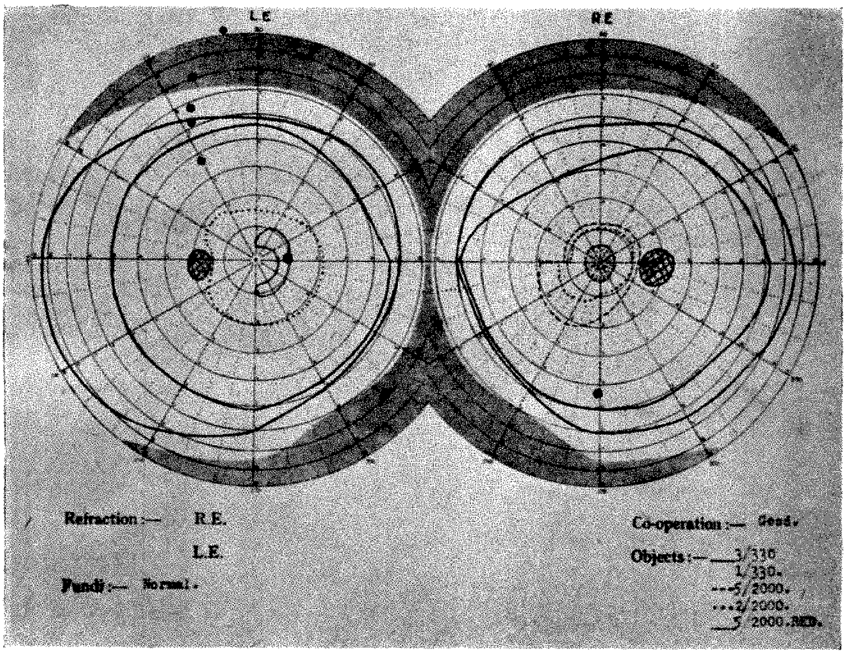

L.E.
R.E.
Refraction :— R.E.
L.E.
Fundi :— Normal.
Co-operation :— Good.
Objects :— 3/330
1/330.
5/2000.
2/2000.
5/2000. RED.

FIG. 5

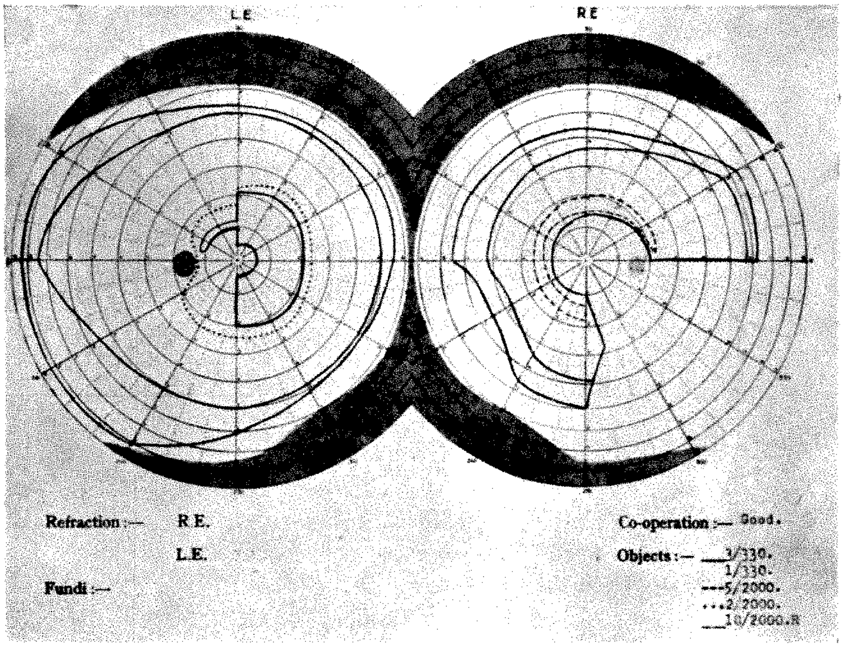
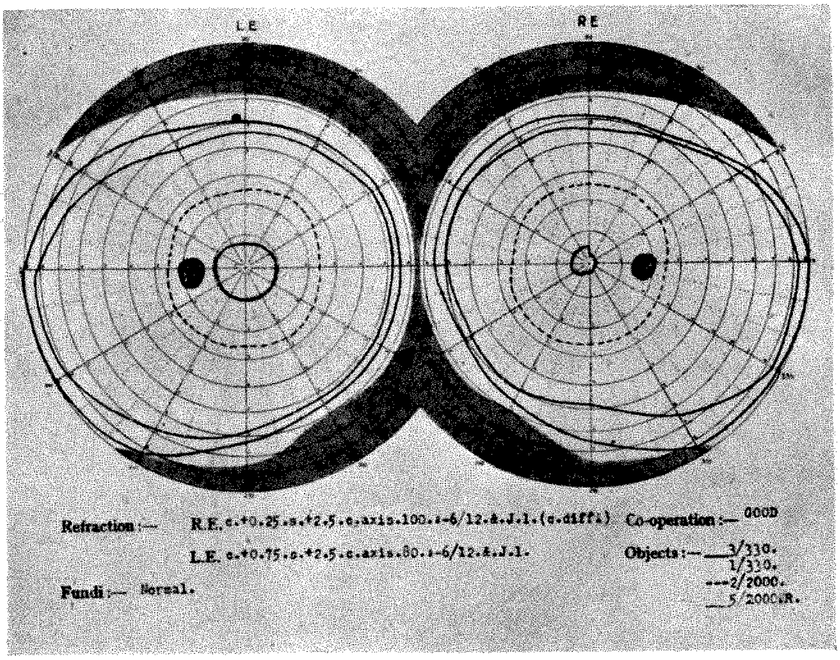

L.E.
R.E.
Refraction :— R.E.
L.E.
Fundi :—
Co-operation :— Good.
Objects :— 3/330.
1/330.
5/2000.
2/2000.
10/2000.R

FIG. 6.

no record of a bilateral central scotoma. It was decided to explore the chiasmal region.

November 9, 1936: Right transfrontal exposure of chiasma. The right optic nerve was straight and normal in appearance. No tumour was seen in the pituitary fossa, but when the chiasma was exposed, a dark rounded tumour appeared just below it. When touched with the forceps it gave the impression of being elastic and tense. Pulsation was not seen. The aneurysm was opened and muscle immediately pushed into the opening. This stopped the voluminous bleeding. The muscle was held in place for fifteen minutes. The flap was then replaced and the wound closed.



Refraction :— R.E. c.+0.25.s.+2.5.c.axis.100.:-6/12.&.J.1.(c.diff.) **Co-operation** :— GOOD

L.E. c.+0.75.s.+2.5.c.axis.80.:-6/12.&.J.1. **Objects** :— ——3/330.

1/330.

---2/2000.

——5/2000.R.

Fundi :— Normal.

Fig. 7.

The patient made a rapid recovery and the headache did not return.

The changes in the visual fields (figs. 5 and 6) were at first alarming, but the final chart (fig. 7) showed complete recovery of vision, and the last report on October 7, 1937, indicates perfect general and visual health.

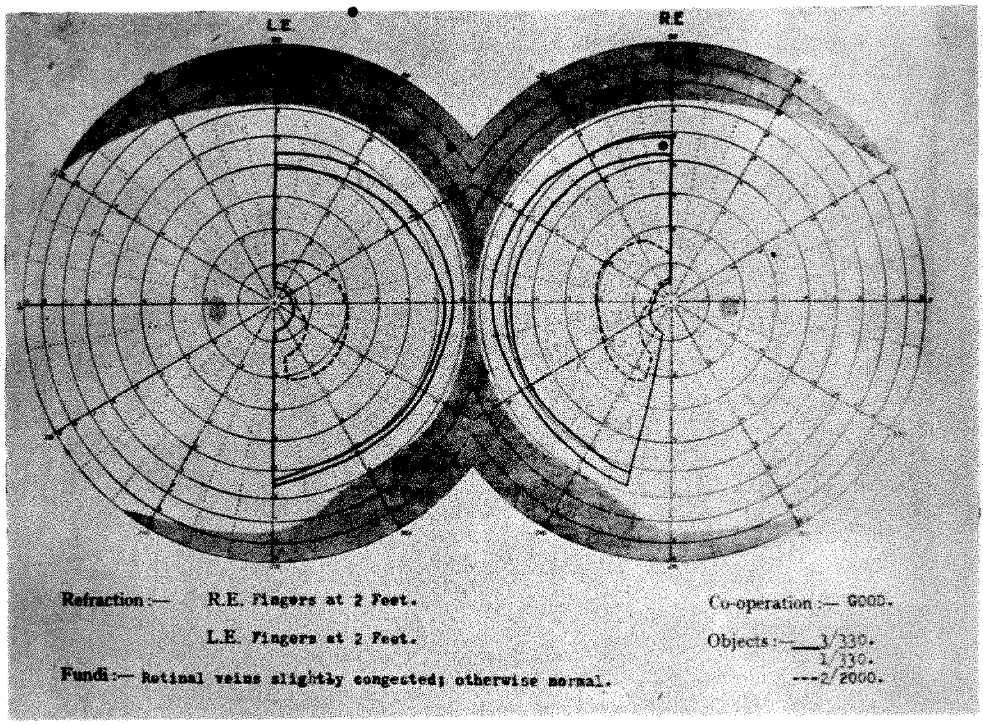
Case 4.—*D. S., female, aged* 49. *Long history of headaches. Recent onset of vomiting, polydipsia and polyuria. Bilateral central scotomata and later bitemporal hemianopsia. Discs normal. Operation, nerves normal, no tumour seen. Post-mortem examination, retrochiasmal tumour.*

The patient was referred to the Richmond Hospital on October 6, 1937, as a pituitary tumour by Dr. R. H. Micks, to whom we are indebted for the following notes.

Previous history.—At the age of 18 she had pleurisy and at 20 she had what was described as exophthalmic goitre. About ten years ago headaches started and have continued. They were described as "pressure on the head."

June, 1936, she began to suffer from excessive thirst and the passage of large amounts of urine, "That was the first thing." At the same time she had bronchitis.

July, 1936, she stated that she was treated in a London hospital for goitre and was given thyroid extract. Vomiting began at this time and made the headache worse.



Refraction:— R.E. Fingers at 2 Feet.
L.E. Fingers at 2 Feet.
Fundi:— Retinal veins slightly congested; otherwise normal.
Co-operation:— GOOD.
Objects:— 3/330.
1/330.
---2/2000.

FIG. 8.

March, 1937, she noticed that the vision of the right side of the right eye was blurred and about a week later that of the left side of the left eye was similarly affected. She occasionally had double vision.

April, 1937, her eyes were examined by Dr. L. Werner who reported: Right eye vision, corrected, $\frac{6}{18}$ centro-cæcal scotoma for colour. Left eye vision, corrected, $\frac{6}{9}$, centro-cæcal scotoma for colour and relative scotoma for white. Fundi normal, peripheral fields full. Because of the history of early impairment of lateral vision special attention was devoted to the peripheral fields, but no defect was discovered in them. Wassermann reaction negative.

Weight 9 st. 8 lb. May, 1937, headache very bad; vomiting. September, 1937, bitemporal hemianopsia and central scotomata.

On admission to the Richmond Hospital the patient appeared dull and apathetic and complained of severe headache. The thyroid gland was not enlarged. General neurological examination was negative. Basal metabolic rate was −1. Average fluid intake 170 oz.; output 130 oz. Blood-pressure 120/85.

Ophthalmological examination.—R.V. fingers at two feet. L.V. fingers at two feet. Discs normal. Visual fields (fig. 8).

Radiological examination by Dr. T. G. Hardman. "The pituitary fossa is deeper than normal but there is no evidence of erosion of its floor or absorption of the clinoid processes. Cranial bones are very thick, particularly in the frontal region in which the appearance is almost suggestive of a hyperostosis. No other abnormality shown."

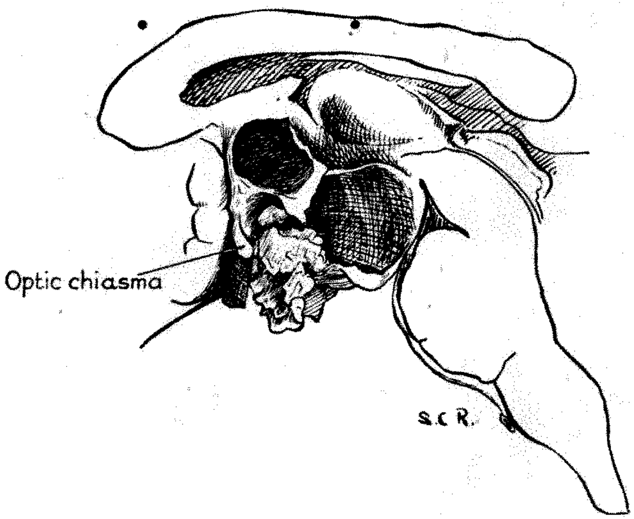


FIG. 9.

October 14, 1937: Operation. Avertin and local anæsthesia. The usual frontal flap for transfrontal exposure of the chiasmal region was made. The bone was over one centimetre thick and had a very irregular inner surface. Passage of the dural separator for the medial section of the bone was difficult and produced excessive bleeding, so that when the bone-flap was turned back the blood-pressure had fallen from 120/80 to 85/55. A saline and glucose intravenous infusion was given and the patient reacted well, but it was considered wiser to postpone the rest of the operation. All bleeding was controlled and the wound closed.

The day after this operation the patient still showed signs of shock. The temperature was subnormal and the thirst and polyuria worse, and she had great difficulty in getting up thick sputum. Within four days she had improved except for a bronchitis which precluded any possibility of a general anæsthetic.

October 18, 1937. Second operation. Local anæsthesia. The bone flap was turned down and the usual exposure of the chiasmal region made. The chiasma was somewhat but not markedly prefixed and the optic nerves short and normal in appearance and course. There was no sign of tumour, nor could one be felt on exploration of the pituitary fossa. As the patient had been very restless all through the operation it was not thought right to split the chiasma and proceed farther, moreover it was thought that a transventricular approach through the foramen of Munro might be better. The wound was then closed.

The pulmonary condition became rapidly worse after this operation and on the third day developed into definite pneumonia. She died two days later.

Post-mortem examination.—The floor of the 3rd ventricle bulged downwards, widening the interval between the optic tracts and displacing the chiasma forwards. The remnant of the pituitary gland was attached to the tuber cinereum. When the optic nerves were drawn downwards the anterior wall of the 3rd ventricle appeared to bulge also and it was embraced by the anterior cerebral arteries.

Fig. 9 shows a drawing of the region in mesial section.

The optic nerves appeared to be normal in every respect.

Microscopic diagnosis: craniopharyngioma. The pituitary gland itself was normal.

The following case may be cited in this connection although the chiasmal region was not inspected during life.

Case 5.—D. J., male, aged 29. Failing vision and photophobia for three years, along with development of acromegalic appearance. Severe headaches. Normal discs. Left homonymous hemianopsia. Greatly expanded sella. Trans-sphenoidal operation. Slight relief. Four months later two attempts to expose growth by transfrontal operation failed because of general pressure. Fatality three weeks after second operation. Post-mortem examination, retrochiasmal tumour of the pituitary gland.

The patient was admitted to the Richmond Hospital, Dublin, on June 26, 1929. Referred by Dr. Greene of Galway as a case of pituitary tumour.

History.—Normal childhood and adolescence. Towards end of 1924 his right eye was struck by a gun trigger. There was some conjunctival hæmorrhage, but the eye was not injured. Libido had been absent for eight years.

In 1925 he began to complain of headaches starting over the right eye and radiating along the right side to the occiput.

In 1926 he noticed he could see more clearly with the right eye closed. About the same time he began to suffer from photophobia. Change in facial appearance began. One attack of epistaxis.

In 1927 there was fluttering of the right eyelid, then the right eyelid closed for five to six weeks, but he could raise it voluntarily a little. Headache off and on till 1927, and ever since then had been continuous.

Examination.—Patient acromegalic in appearance, mandibular prognathism, slight build otherwise. Complains of increasing drowsiness. All movements slow and deliberate, it takes him about one and a half hours to get dressed. Hands enlarged, subcutaneous tissue thickened. Height 5 ft. 9½ in. Weight 126 lb. Blood-pressure 120/80. Urine normal in quantity and quality. Wassermann reaction negative.

The positive neurological findings were as follows: Visual acuity right eye $\frac{6}{6}$ with plus 0·5 lens, left eye $\frac{6}{6}$. Discs normal. Left homonymous hemianopsia. Outward rotation of the eyes normal; inward rotation almost absent, up and down movements very defective. Right pupil larger than left; both react to light and accommodation. A very slight proptosis of the right eye was first noticed in February, 1930. The outlines of the floor of the sella turcica were obliterated and the clinoid processes were widely separated. Resting blood sugar, 0·06 per cent.; after 50 grm. of glucose, 0·09 per cent.

Operation.—March 9, 1930. A trans-sphenoidal operation was performed and some tumour tissue removed. After this operation the patient said that the headache was modified, but was still present. He was treated with deep X-ray therapy, but in the course of two months the headaches returned with greater intensity than ever, and he suffered from extreme photophobia and constant lacrymation.

On June 24, 1930, a right transfrontal exposure of the tumour was attempted but the general intracranial pressure was so extreme that it was impossible to reach the growth in spite of the free use of hypertonic salt solution and glucose. No fluid could be obtained from the ventricles. A large decompression was left. There was but a transient improvement after this operation, and on July 14, 1930, after the administration of hypertonic salt solution and lumbar puncture, a second attempt was made. This proved as futile as the first and had to be abandoned because of the actual bulk of the brain. The patient survived this operation for twenty-one days.

Post-mortem examination.—A tumour about the size of a tangerine orange occupied the peduncular region. The right crus was flattened and appeared twice the width of the left. The right optic tract was flattened out against the crus. The chiasma itself stretched like a bridge between the crura; it was oval rather than flat. The optic nerves were normal in appearance and the tumour had not filled the interval between them.

Microscopic diagnosis: adenocarcinoma.

These cases suggested that normal discs might indicate a retrochiasmal tumour, but the following case showed that normal discs might be found when the tumour was prechiasmal.

Case 6. *D. H., male, aged* 21. *Acromegaly. Headache and vomiting for last year. Diplopia. Normal discs. Bitemporal hemianopsia. Gross enlargement of pituitary fossa. Operation, pituitary tumour. Death. Post-mortem examination, prechiasmal tumour.*

The patient was referred to the Richmond Hospital, Dublin, on October 13, 1936, by Dr. Keane, of Belfast, on account of severe headache and vomiting.

The patient began to suffer from headaches accompanied by vomiting a year before admission. About the same time he began to " see double." The headaches steadily increased in severity until they became unbearable. There were occasionally periods of polydipsia and polyuria vaguely remembered.

Examination.—Acromegalic. Height 5 ft. 11 in. Weight 9 st. Blood-pressure 125/60. Basal metabolic rate −12. Mentally dull. Average urinary output was 80 oz. No excessive thirst. Neurological examination negative.

Opthalmological examination revealed normal discs and a complete bitemporal hemianopsia with macular sparing.

The pituitary fossa was grossly enlarged.

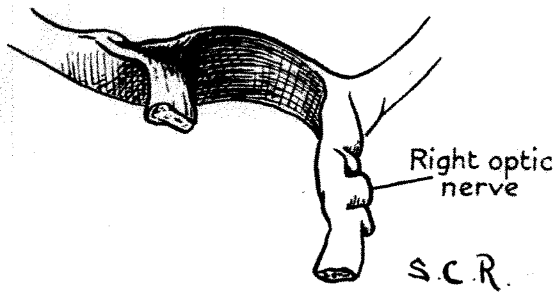


FIG. 10.

November, 1936, he was given a course of deep radiotherapy which had no effect on the headache or vomiting.

January 21, 1937, readmitted in a pitiable condition. The headaches were extremely severe and he had become more sluggish and stupid and occasionally incontinent.

It was decided to make an attempt to relieve the headaches.

March 25, 1937, ventriculography revealed marked dilatation of the lateral ventricles which communicated freely through an opening in the septum lucidum. The 3rd ventricle was not shown.

Operation.— Right transfrontal exposure of the chiasmal region. The right optic nerve was straight and was not displaced laterally. The middle of the pituitary fossa was occupied by a tumour which was attacked by the diathermy loop. A large amount of tissue was removed until the fossa appeared to be empty. The chiasma was not seen. The patient never regained consciousness after the operation and he died eighteen hours afterwards.

Post-mortem examination revealed that the lower third of a column of tumour had been removed and that the upper two-thirds had been left behind.

This upper part of the growth had pushed the chiasma and the anterior wall of the 3rd ventricle backwards and had burrowed into the right frontal lobe just below the genu of the corpus callosum. This depression measured 2½ by 2 cm., and was 2 cm. deep. The chiasma itself was reduced to a mere ribbon, but neither optic nerve was flattened (fig. 10). The right nerve was deeply indented on its upper and lateral aspect by the right anterior cerebral artery. Across the base of the upper surface of the left optic nerve there was a deep groove which seemed to cut the nerve off from the chiasma, leaving only its attachment to the optic tract.

It is noteworthy that gross notching of the optic nerves by vessels did not produce pallor of the discs nor did it seem to account for the defects recorded in the visual fields. Those defects were explained by the chiasmal lesion itself.

Although the tumour in this case was prechiasmal, it differed from the usual type of this tumour in that it did not displace the optic nerves laterally.

Microscopic examination: eosinophile adenoma.

DISCUSSION.

This study has been confined to cases which presented visual field defects and in which the relation of the tumour to the chiasma has been verified.

All the cases reported above had unequivocal symptoms and signs of a tumour in the neighbourhood of the chiasma and all had normal discs. During the period in which these cases were encountered there were eight patients with similarly definite symptoms and signs of tumour in the same situation, in whom there was primary optic atrophy.

In the group with normal discs the optic nerves in each case were normal in appearance and ran straight from the optic foramina to the chiasma. In Cases 1 and 6 the optic nerves had one or more deep notches apparently due to pressure against arteries. These notches were not seen during the operation. In the group with primary optic atrophy, the nerves appeared to be whiter than normal, to be flattened and to curve round the tumour tightly embracing it.

In the first group five of the six tumours were retrochiasmal; the sixth was prechiasmal but of an unusual type.

In the second group all the tumours were prechiasmal.

It would appear that pallor of the discs in cases of tumour in this region is related to displacement or stretching of the optic nerves rather than to any kind of involvement of the optic chiasma or optic tracts, and that the nerves are more likely to be free from embarrassment when the tumour lies behind the chiasma than when it lies in front of the chiasma.

In our experience the meningioma which grows from the tuberculum sellæ is constantly associated with pallor of the discs.

The high proportion of retrochiasmal tumours to prechiasmal in our series calls for comment. In this country slight defects of vision often pass unnoticed by the patient and grave defects are borne with fatalistic equanimity as long as pain is absent. Not one of the patients whose histories are given in this paper, not even the blind one, came to hospital because of failing vision; each came because of pain in the head. Retrochiasmal tumours are more often associated with severe headache than are prechiasmal tumours.

The difference in operative mortality between the two groups is very marked. In the first group with normal discs four out of six patients died. In the group of prechiasmal tumours with primary optic atrophy one patient out of eight died.

SUMMARY.

In five of six cases of tumour involving the chiasma in which the optic discs were normal, the tumour was behind the chiasma. In the sixth case the tumour was of an unusual prechiasmal type.

CONCLUSION.

When the optic discs in a patient with chiasmal symptoms are pronounced normal by an experienced ophthalmologist, it is probable that the lesion, if a tumour, will be found behind the chiasma.

THE NEURONE AS STUDIED BY MICRO-INCINERATION.

BY LEO ALEXANDER, M.D. (BOSTON, MASS.)[1]

THE micro-incineration method, first conceived by Raspail (1833) developed and perfected by Policard (1923) and Scott (1933, 1933-34), is capable of contributing certain data concerning the structure of the neurone. These data can be divided into three groups :—

(1) Intraneuronal differences in the content of heat-resistant minera ash.

(2) Interneuronal differences in the content of heat-resistant mineral ash.

(3) Differences in the content of heat-resistant mineral ash exhibited by the same part of the same neurone during different phases of ontogenetic development.

(1) INTRANEURONAL DIFFERENCES.

There are differences in the distribution of the heat-resistant mineral ashes over the various parts of the neurone. The ganglion cells contain considerable mineral deposits in their nucleoli, their cytoplasm and their dendrites (fig. 1). The nucleus is essentially free from mineral residue except for some fine granular strands, especially along the nuclear membrane. The mineral deposits in the cytoplasm are globular and granular in character and correspond in their arrangement to the Nissl bodies. They contain calcium, very little iron, and some water-soluble minerals. The nucleolus, in addition, contains some doubly refractive silica ash. The intracellular neurofibrillæ are completely free from mineral ash (fig. 1). The axone hillock and axis cylinder are completely free of the heavy ash of calcium, iron or silica, and in most well incinerated preparations are free from any heat-resistant mineral ash (Scott, 1933, Alexander and Myerson, 1937). In some specimens, however, here and there some faintly visible mineral granules of bluish colour are seen in the axone hillock and axis cylinder. These granules are soluble in water and are not completely heat resistant because they are usually not present in well incinerated preparations, being vaporized or volatilized at or below the heat of micro-incineration (650° C.).

---

[1] From the Division of Psychiatric Research, Boston State Hospital, and the Department of Neurology, Harvard Medical School, Boston, Mass.

Aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

In the peripheral nerves the axis cylinder either burns out completely or leaves only a faint trace of fine bluish granules, which are vaporized or volatilized easily at higher temperatures. Fig. 2 illustrates these facts in a cross-section from the peripheral nerve of a healthy pigeon. The network of heavy-ash residue corresponds to the endoneural and Schwannian sheaths, the heaviest, white, water-soluble ash residue being that of the nuclei of the Schwannian cells while the endoneural network and the processes of the Schwannian cells, contain somewhat less. A fine, thin, inner layer of much less brightly illuminated ash corresponds to the thin outer membrane of the myelin sheath which is closely adjacent to and, in many places, seems to merge with the cell bodies and processes of the Schwannian cells. The central cores of this honeycombed network, which consists of the endoneural and Schwannian sheaths and at their inner side a thin, outer membrane of the myelin sheath, are occupied, as seen in stained neighbouring sections, by the lipoid body of the myelin sheath, and the axis cylinder. In micro-incinerated preparations, however, the lipoid body of the myelin sheath never leaves

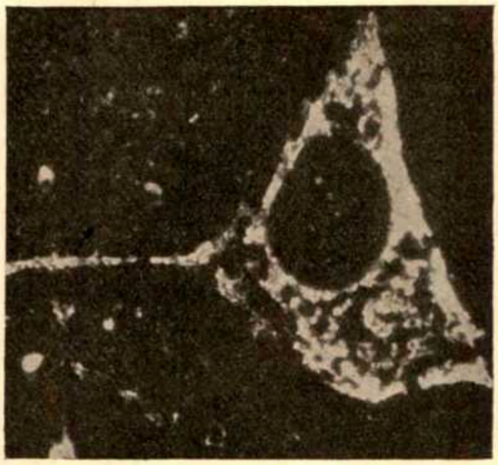


FIG. 1.—Normal motor ganglion cell from anterior horn of spinal cord. Cat. Darkfield illumination. Enlargement × 1300.

any trace at all; it is always burned out completely without leaving mineral-ash residue. Also the axis cylinder, in many instances, has burned out, thereby leaving the central cores of many meshes of the honeycombed sheath-network completely empty. In other instances, however, either in the centre or somewhat eccentrically in the central core, a small round, elliptic or polygonal body, consisting of an accumulation of fine, faintly visible, bluish mineral granules is seen which corresponds, as stained neighbouring sections show, to the axis cylinder. In some instances, one sees that from the margins of the discs of ash residue, which the cross-sections through the axis cylinders represent, especially from the corners of the polygonal ones, fine threads (2 to 5) of equally faint bluish ash granules extend to the outer membrane of the myelin sheath. These threads, which connect the axis cylinder to the outer membrane of the myelin sheath, are part of the myelo-axostroma of Kaplan (1902). (The myelo-axostroma is not to be mistaken with neurokeratin net, which, especially since Kaplan, has been regarded generally as an artefact.) In some suitable preparations, the observation can be made that those fine ashes, which comprise the trace of the axis cylinder in micro-incinerated preparations, are more dense along the outer membrane of the axis cylinder, the axolemma, than in the interior of the axis cylinder. These findings can best be seen in preparations which are at the border-line of complete incineration. In very thoroughly incinerated preparations, the mineral residue of the axis cylinder is vaporized or volatilized; the ash residue of the myelo-axostroma, however, usually remains.

In the peripheral nerves of the frog, the axis cylinder always burns out completely and is invisible in micro-incinerated preparation. Fig. 3 shows a longitudinal section through the sciatic nerve of the frog. The Schwannian cells are well outlined by their bright white ash residue, as are the endoneural and Schwannian sheaths. All the central cores of the nerve fibres which correspond to the axis cylinders are empty and free from ash residue. The outer parts of these central cores which correspond to the myelin sheaths can be seen transversed by a fine, loose meshwork corresponding to the myelo-axostroma, somewhat heavier threads of which outline the rings of Ranvier and Lantermann's incisures. Several of these are well recognizable in fig. 3. The lipoid part of the myelin sheath contained within the meshes of the myelo-axostroma is free from mineral ash residue.

In the central nervous system in man, axis cylinders usually do not leave any traces in well incinerated preparation. Figs. 4 and 5 show a part of the optic tract from a 36-year-old man at various enlargements. Most outstanding in their mineral content, consisting for the most part of white water-insoluble ashes, are the nuclei of the glial cells (fig. 4). Somewhat less ash is found in the glial reticulum and in the outer lamellæ of the myelin sheaths. At somewhat higher enlargement, one sees that the lines which the myelin sheaths represent in micro-incinerated preparations are not quite straight or of equal density and calibre, but show numerous varicose excrescences which gives them a somewhat dotted appearance. At still higher power, one recognizes that these highly-mineral containing dots are fibrillary processes of glial cells which pass and adhere to the myelin sheaths at various irregular intervals, embedding them in an irregular network of reinforcements by fibrillary glial processes (fig. 5). These glial reinforcements of the myelin sheaths vary somewhat within the central nervous system. They are most dense and numerous in the central white matter of the hemispheres, less dense in the optic nerve and tract and in the long projection pathways of the brain-stem, while they are of the least density in the white columns of the spinal cord. Their number determines the amount of mineral ash which the white substance presents in micro-incinerated preparations at low enlargement. Compared to the ash content of these glial reinforcements, the outer membrane of the myelin sheath is poor in heat-resistant mineral ash (fig. 5). The central core inside of the outer membrane of the myelin sheath can be seen to be transversed by rather loosely arranged, faintly visible trabeculæ corresponding to the myelo-axostroma. The axis-cylinder itself, and the main lipoid body of the myelin sheath, however, are free from mineral ash. Scott gave a drawing from the sciatic nerve of the cat (fig. 43, plate III), which he did not describe in the text, to which our fig. 5 is very similar.

The musculature is moderately rich in bluish and white, water-soluble and water-insoluble mineral ashes, decidedly less rich than ganglion cells, but much richer than the myelo-axostroma of the nerve fibres. We have not yet been able to identify nerve-endings in micro-incinerated preparations.

In summary it may be concluded:—

(1) Ganglion cells contain rich deposits of heat-resistant mineral ashes in the Nissl bodies of their cytoplasm and their dendrites, and in their nucleolus.

(2) The axone hillocks, the axis cylinder processes, and the main body of the axis cylinders of the central and peripheral nervous system

are completely free from calcium, silica and iron, and are free from other heat-resistant mineral ashes, but contain fine traces of not completely heat-resistant minerals, which are vaporized or volatilized at or below the heat of micro-incineration (650° C).

(3) The myelo-axostroma, including the tubular outer membrane of the myelin sheath, the axolemma, and the connecting threads and lamellæ between them, in the central and peripheral nervous system, contains a small amount of bluish heat-resistant mineral ashes.

(4) The lipoid part of the myelin sheath is always completely free from any mineral ash residue.

(5) The glial reticulum, in which the central nervous structures are embedded, and the Schwannian and endoneural sheaths of the peripheral nervous system, contain moderate amounts of heat resistant mineral ash, the richest accumulation of which is found in the nuclei of glial and Schwannian cells. The glial reticulum in which myelinated nerve fibres are embedded and its ash residue are most dense in the white matter of the hemisphere, less dense in the long projection pathways of the brain-stem, including the optic tract, least dense in the white columns of the spinal cord.

(2) INTERNEURONAL DIFFERENCES.

Differences in amount and quality of mineral deposits are not only found between ganglion cells of dissimilar morphology, such as between spinal ganglion cells, pyramidal ganglion cells and anterior horn cells (Scott, 1933, Alexander and Myerson, 1937), but also between ganglion cells which are, when studied by the ordinary staining methods, of very similar shape and structure, such as the granular cells of the cerebrum and the cerebellum respectively (Alexander and Myerson). The granular cells of the cerebellum are extremely rich in mineral deposits—calcium as well as iron—while the cortical granular cells from the fourth layer of the isocortex are very poor in mineral residue. This is illustrated by figs. 7 and 8. Fig. 7 shows a section through the central region of the cerebral cortex of a 43-year-old man, including anterior and posterior-central convolutions adjacent to the sulcus centralis Rolandi. The anterior central convolution (a) is extremely rich in white, water-insoluble mineral ash residue, contained in its small and large pyramidal ganglion cells, while the posterior central convolution (p), the ganglion cells of which are of granular type (coniocortex, Economo, 1930), contains comparatively little ash residue. In comparison to the granular cells of the posterior central convolution, however, the granular cells of the cerebellar cortex from the same individual are very rich in heavy, white mineral ash. This difference does not only apply to the granular layers of the cerebrum and the cerebellum as a whole, but also any single granular cell from the cerebellum is richer in mineral ash than a single granular cell from the cerebral cortex.

This fact can also be well demonstrated in small animals, which present the advantage that one sagittal section through the entire brain can be incinerated on one slide (fig. 6). This eliminates the possible error of difference in thickness and in degree of incineration between different slides. Fig. 6 shows a sagittal section through the brain of a normal adult guinea-pig. The granular layer of the cerebellar cortex is much richer in ash residue than the isocortex of the cerebral hemispheres. The allocortical areas of the fore-brain, however, are much richer in mineral ash than the isocortical areas. Most outstanding in rich mineral content are the cells of the fascia dentata (fd) ; next are the main allocortical areas at the base of the brain, the tuberculum olfactorium (to), the area prepyriformis (pr), and the area retrobulbaris (rb). (The nomenclature used is that of Rose (1926-27*a*, 1926-27*b*, 1927-28, 1929-30, 1931).) The granular cells of the cerebellum, however, are richer in mineral residue than the cells from the allocortical areas, with the possible exception of the fascia dentata and the area prepyriformis ; but this needs furthur investigation by exact quantitative studies. Thalamus and striopallidum are comparatively poor in mineral content. The richer mineral content of the granular layer of the cerebellum, as compared to the cerebral hemispheres and the striopallidum, is also striking in the pigeon and the cat. The granular cells of the cerebellum are not only found richer in mineral residue when completely incinerated, but also are more difficult to incinerate than other ganglion cells. If whole brain sections are incinerated, the cerebellum is the last part to become incinerated completely. This finding points to the fact that other constituents which also determine the speed of incineration, notably proteins, may be of a different nature in the granular cells of the cerebellum, since they more frequently and easily form tarry residues in these than in other cells of the central nervous system. In the cat the area prepyriformis (pr) is outstandingly rich in white mineral ash as compared to the isocortical areas, for example the area precentralis granularis (pg), in the same section (fig. 9). In the olfactory bulb, the cells of the inner granular layer are richer in mineral residue than those of the outer granular layer (fig. 9 bu) ; the stratum granulosopyramidale (pyramidale internum) and the stratum pyramidale externum contain much less; the inner and outer molecular layers are practically free from heat-resistant mineral ashes. This distribution of the heat-resistant mineral ashes in the olfactory bulb is positively correlated with the depth of colouring which these layers present in Nissl-stained preparations (compare our fig. 9 to corresponding Nissl-stained preparations given in Rose's atlas).

These differences in heat-resistant mineral ash exhibited by the various types of neurones in the central nervous system of man and animals will have to be studied in more detail by methods which permit a more accurate qualitative and quantitative analysis. These data, gained by micro-incineration, give a lead in this direction. Especially the constancy of greater ash content of cerebellum and allocortex, as compared to isocortex, thalamus and striopallidum throughout the phylogenetic series, is of interest and may bear a certain relationship to functional constancy.

(3) DIFFERENCES IN THE CONTENT OF HEAT-RESISTANT MINERAL ASH EXHIBITED BY THE SAME PART OF THE SAME NEURONE DURING DIFFERENT PHASES OF ONTOGENETIC DEVELOPMENT.

Embryonic tissue, as well as tumour tissue, is richer in heat-resistant mineral ash than normal differentiated adult tissue (Horning and Scott, 1932; Scott and Horning, 1932; Alexander and Myerson, 1937). For the neurones of the human central nervous system, Alexander and Myerson have demonstrated that the cortical ganglion cells of the new-born child are richer in heat-resistant mineral ash than those of the adult; most of this ash, however, is contained in the nuclei of the ganglion cells of the new-born, while their cytoplasm contains only small amounts of it (Alexander and Myerson, plate lxiii, fig. 1). Differences of the ash content in the various cortical areas during ontogenetic development have been studied in a series of brains from the fœtal and the new-born cat and of kittens during the first three weeks of life. Sagittal sections were cut in order to be able to incinerate as many different parts of the brain as possible on one slide at the same time. Fig. 10 shows an incinerated sagittal section through the entire brain of the new-born cat at low enlargement. The cerebellar cortex and various areas of the allocortex, notably the cornu ammonis (c), the area entorhinalis (e) and the area prepyriformis (pr), stand out by their rich ash content, as they do in the adult: but, in addition, two areas of the isocortex are well and sharply outlined by their exceedingly rich content of heat-resistant mineral ash, namely, the area striata (str) and the anterior central region (ac). These two areas are in the process of most active growth at that time, and they are the first two areas of the isocortex to undergo myelinization (primordial areas) (Flechsig, 1901, v. Monakow, 1914). According to Flechsig, myelinization occurs first in the central region, second in the fascia dentata, the uncus gyri hippocampi and other allocortical regions, third in the cornu ammonis, fourth in the area striata. In the newborn cat, also, the thalamus and the striopallidum are relatively richer in heat-resistant mineral ash than in the adult.

Within the same area, and within the same type of neurone, the more primitive cells are richer in heat-resistant mineral ash than those which have already reached higher differentiation. This fact is best illustrated in the cerebellar cortex of the newborn, mammalian as well as human, owing to a peculiarity of the topographic arrangement of its still-proliferating primitive, and its differentiated cells, which has been well described by Ramón y Cajal (1890*a*), Lugaro (1894*a*), Schaper (1894), Biach (1909-10), Löwy (1909-10) and Obersteiner (1912).

The matrix of the cerebellar cortex, at about the middle of embryonic life in man, splits in an outer and an inner granular layer, separated by the anlage of the molecular layer. While the cells of the inner granular layer undergo early differentiation and cease to proliferate, the cells of the outer granular layer at the outer surface of the cerebellar convolutions retain their primitive medullo-blastic character up to the eighth or ninth month of intrauterine life, continue to proliferate and to supply, among other cells, additional neuroblasts which continuously migrate through the molecular layer into the inner granular layer where they undergo differentiation into cerebellar granular cells. Thus, for a long period, the outer granular layer remains the matrix (secondary matrix) of the granular layer of the cerebellar cortex, consisting of undifferentiated, actively proliferating cells, while the differentiated cells accumulate in the inner granular layer. In the newborn, these two layers are clearly separated by the intervening molecular layer (Obersteiner, fig. 232, page 611). In micro-incinerated preparations of the cerebellum of the newborn cat, as well as of the newborn human infant (fig. 11), the immature outer granular layer (og) is much richer in heat resistant, water-insoluble mineral ashes than the mature, differentiated, inner granular layer (ig). Not only the outer granular layer as a whole, but each individual cellular element of the primitive outer granular layer is richer in white, brightly luminous ash than the individual differentiated cellular elements of the inner granular layer. This finding justifies the conclusion that neurones during active growth and ontogenetic development are relatively richer in heat resistant mineral ashes than after differentiation.

CONCLUSIONS AND SUMMARY.

(1) Ganglion cells contain rich deposits of heat resistant mineral ashes in their nucleolus and in the Nissl bodies of their cytoplasm and dendrites.

(2) The intracellular neurofibrillæ, the axone hillock and the main body of the axis cylinder are free from heat-resistant mineral ashes.

(3) The lipoid part of the myelin sheath is free from mineral ash.

(4) The myelo-axostroma contains a small amount of heat-resistant mineral ash.

(5) The granular cells of the cerebellar cortex and the ganglion cells from allocortical areas are richer in mineral ash residue than morphologically similar ganglion cells from isocortical areas or from the basal ganglia. In addition, there is a great deal of variation in the mineral distribution corresponding to cortical architectural fields.

(6) The content of heat-resistant mineral ash in the same neurone is relatively greater during ontogenetic development than after differentiation.

(7) The fact that the content in heat-resistant mineral ashes is greater in ganglion cells than in nerve fibres, and relatively greater in ganglion cells during ontogenetic development than after differentiation, suggests a positive correlation of these heat-resistant mineral ashes with growth and with metabolic activity.

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PLATE II.

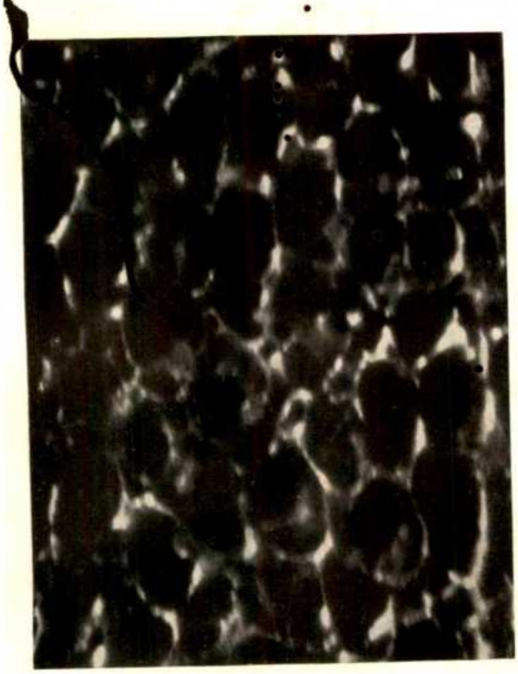

FIG. 2.

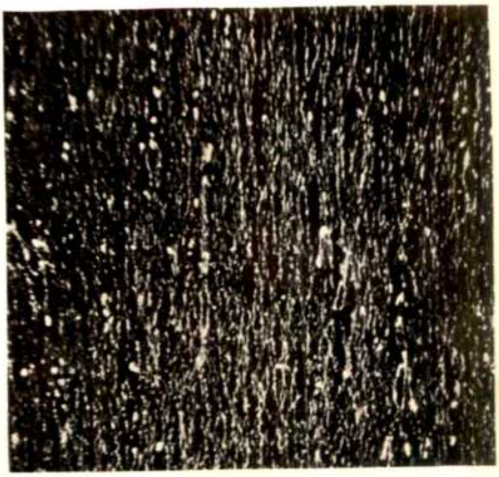

FIG. 4.

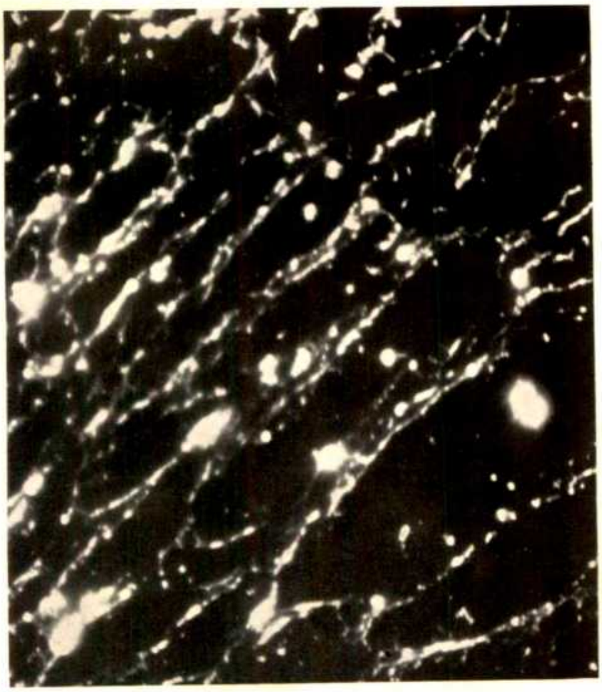

FIG. 3.

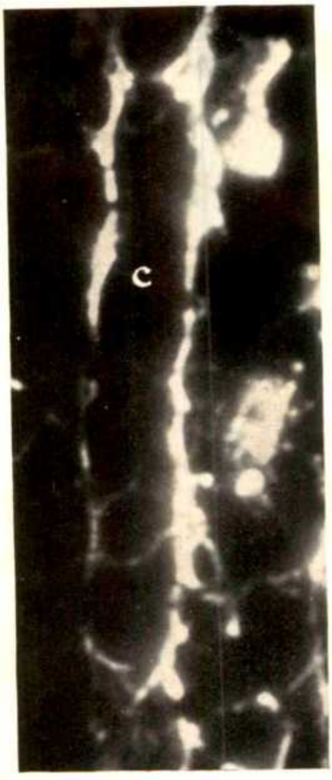

FIG. 5.

To illustrate paper by Leo Alexander.

PLATE III.

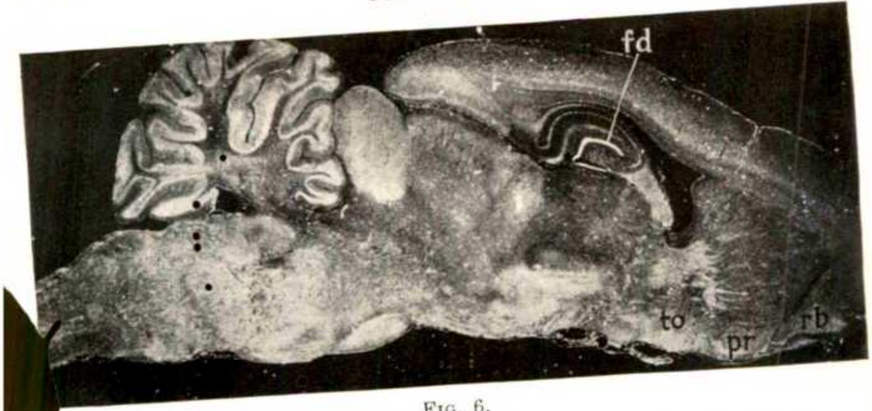

FIG. 6.

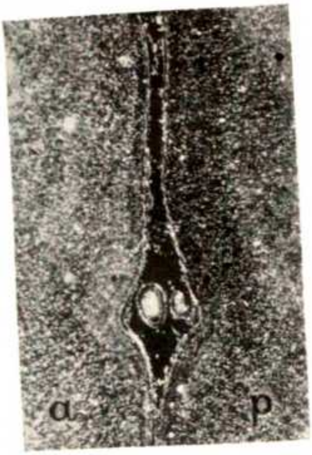

FIG. 7.

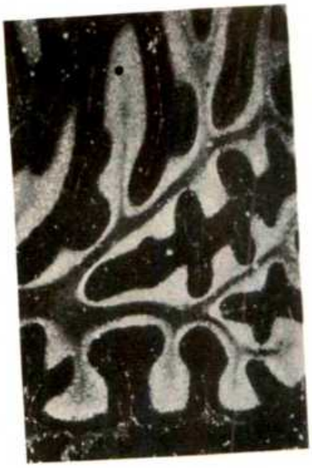

FIG. 8.

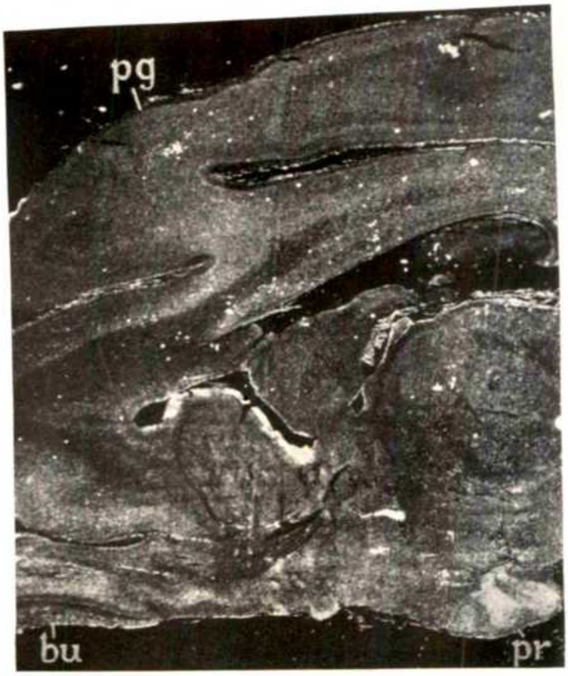

FIG. 9.

To illustrate paper by Leo Alexander.

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LEGENDS.

Fig. 2.—Transverse section through peripheral nerve (wing nerve) of a healthy pigeon. Darkfield illumination. Enlargement × 1300.

Fig. 3.—Longitudinal section through peripheral nerve (sciatic nerve) of a frog. Darkfield illumination. Enlargement × 1300.

Fig. 4.—Longitudinal section through the optic tract of a 36-year-old man. Darkfield illumination. Enlargement × 175.

Fig. 5.—A myelinated fibre from the optic tract shown in fig. 4 at higher enlargement. Darkfield illumination. Enlargement × 2210. c = central core of the nerve-fibre, occupied by the axis cylinder and the inner lipoid part of the myelin sheath, which are free from mineral ash residue. In the lower half of the figure the central core of the nerve-fibre is seen to be transversed by a few fine threads which are part of the myelo-axostroma.

Fig. 6.—Sagittal section through the brain of a normal guinea-pig. Oblique transillumination. Enlargement × 7. fd = fascia dentata, pr = area prepyriformis, rb = area retrobulbaris, to = tuberculum olfactorium.

Fig. 7.—Section through the anterior and posterior central convolutions of the normal human cerebral cortex and the intervening sulcus centralis, Rolandi. 43-year-old man. Oblique transillumination. Enlargement × 8. a = anterior central convolution, p = posterior central convolution.

Fig. 8.—Section through normal cerebellar convolutions. 43-year-old man. Oblique transillumination. Enlargement × 8.

Fig. 9.—From a sagittal section through the brain of a newborn cat. Oblique transillumination. Enlargement × 7. bu = olfactory bulb, pg = area precentralis granularis, pr = area prepyriformis.

Fig. 10.—Sagittal section through the brain of a new-born cat. Oblique transillumination. Enlargement × 7 ac = anterior central region, c = cornu ammonis, e = area entorhinalis, pr = area prepyriformis, str = area striata.

Fig. 11.—Convolutions of the cerebellum of the new-born human infant. Darkfield illumination. Enlargement × 80. ig = inner granular layer, m = anlage of the molecular layer, og = outer granular layer, w = central white matter of cerebellar convolution.

THE ORIGIN OF THE FALL IN THE PRESSURE OF THE CEREBROSPINAL FLUID AFTER ITS ARTIFICIAL ELEVATION BY JUGULAR OCCLUSION.

BY T. H. B. BEDFORD.

(*From the Department of Pharmacology, Manchester University.*)

THE effect of jugular occlusion on the cerebrospinal fluid pressure in the cisterna magna and on the venous pressure in the torcular has been described in earlier papers (Bedford, 1935, 1936). It was found that the rise in the pressure of the cerebrospinal fluid which follows sudden occlusion of the external jugular veins is a temporary phenomenon, and that the pressure usually returns to the region of its original level within the space of one hour. The venous pressure in the torcular was also observed to fall, but the fall was not so rapid or so complete as the fall in the pressure of the cerebrospinal fluid, and at the end of the experiment the torcular venous pressure was sometimes more than twice its original height. These pressure changes were found to occur independently of variation in the systemic arterial pressure. The average duration of the experiments was two hours. It was concluded that the fall in the pressure of the cerebrospinal fluid was due mainly to the establishment of collateral venous circulation. It was considered, however, that there had been also a reduction in the total volume of the cerebrospinal fluid. In the experiments which are to be described, an attempt has been made to study the problem by observing the effect of jugular occlusion on the rate of absorption of isotonic solution from the subarachnoid space.

EXPERIMENTAL PROCEDURE.

The general experimental procedure and the methods employed to record the intracranial pressures were identical with those used in earlier experiments (Bedford, 1935, 1936). The manometer in the cisterna magna was, however, connected by a three-way tap with a device by which the pressure of the cerebrospinal fluid could be maintained at any desired level and the rate of inflow or of outflow of fluid from the subarachnoid space determined. The apparatus employed for this purpose was modelled on that used by Mortensen and Weed (1934) in their study of the absorption of isotonic solution from the subarachnoid space. These workers have given a detailed description, including a diagram of their apparatus. It is unnecessary, therefore, to give more than a brief account here. The apparatus consists of a reservoir of large diameter, containing isotonic saline solution, which can be raised or lowered. The diameter of the reservoir is sufficiently large to ensure that the maximum volume of fluid likely to enter or to be expelled from the subarachnoid space during the period of an experiment will have no appreciable effect on its fluid level. The pressure of the cerebrospinal fluid can, therefore, be maintained at any desired level by setting the reservoir and putting it into communication with the needle in the cisterna magna. A device consisting of two vertical graduated pipettes is interposed between the reservoir and the three-way tap. The upper half of each pipette and the connecting tubing is filled with a paraffin-chloroform mixture coloured with Sudan III. This mixture has the same specific gravity as the saline solution. The volume of fluid passing from the external system into the animal or extruded under conditions of constant pressure can be determined by observing the meniscus between the paraffin-chloroform mixture and the saline solution. The oily mixture may occasionally stick to the sides of the pipettes or retract unevenly during rapid extrusion or inflow of fluid, and thus render accurate reading impossible. Two pipettes are employed merely to ensure that one meniscus at least is available for reading. The only modification introduced into this apparatus has been the replacement of rubber connections by glass where possible. The saline solution used in these experiments was Tyrode's solution.

(1) *The effect of jugular occlusion on the absorption of isotonic solution from the subarachnoid space when the reservoir is set at the pressure level assumed by the cerebrospinal fluid.*

The normal pressure of the cerebrospinal fluid and the venous pressure in the torcular were first determined. The external jugular veins were then occluded and the new pressure levels noted. After a preliminary pause of some two or three minutes, the reservoir was set at a pressure corresponding with that of the cerebrospinal fluid and put into communication with the subarachnoid space. The rate of inflow or of outflow of fluid was observed over a period of one to one and a half hours. Fifteen experiments were performed. A fairly typical experiment is represented in fig. 1. The relative stability of the venous pressure after the pressure of the cerebrospinal fluid had once been fixed was a striking feature of these experiments. The venous pressure in the torcular at the end of the experiment was often identical with that observed at the beginning. A pronounced fall in venous pressure was generally associated with a fall in the systemic blood pressure and

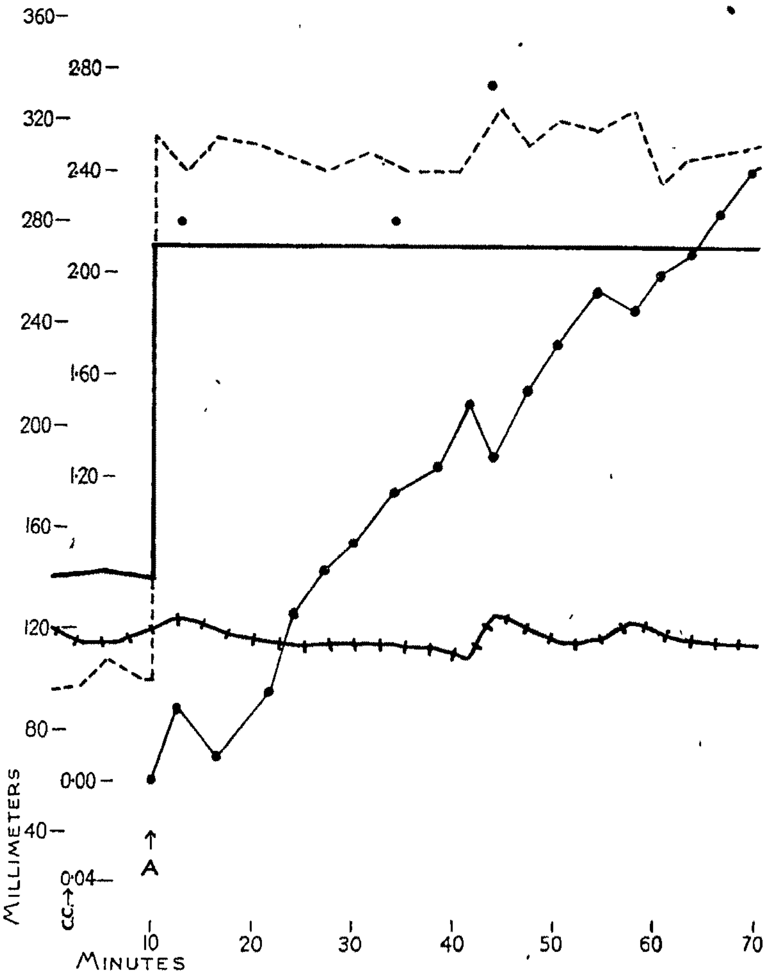

FIG. 1.—The effect of jugular occlusion on the absorption of cerebrospinal fluid when the reservoir is set at a pressure level corresponding with that assumed by the cerebrospinal fluid. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of Tyrode solution, that in the femoral artery in millimetres of mercury. The external volume is recorded in cubic centimetres of Tyrode solution. The veins were occluded and the cerebrospinal fluid pressure maintained at A.

————	Cerebrospinal fluid pressure.
– – – – –	Venous pressure in torcular.
–●–●–	External volume change.
- -+—+—	Systolic pressure in femoral artery.

an experiment was not considered successful unless the systemic arterial blood-pressure was maintained. A flow of fluid from the external system into the animal was observed in all experiments. This persisted even when the venous pressure rose, although sudden changes in the venous pressure were temporarily reflected in the rate and occasionally in the direction of flow. The average rate of flow in fifteen experiments was 0·049 c.c. per minute. In some of the experiments, however, there was a moderate fall in the venous pressure in the torcular. This would bring about a decrease in the total volume of the intracranial venous system and cause a flow of fluid from the reservoir into the animal. The rate of inflow was accordingly relatively greater in these experiments than in those in which the venous pressure was maintained.

(2) *The effect of jugular occlusion on the absorption of isotonic solution when the pressure of the cerebrospinal fluid is maintained at its original level.*

The pressure of the cerebrospinal fluid was first recorded until its level became reasonably steady. The reservoir was then set at that level and put into communication with the subarachnoid space. Under these circumstances fluid should neither enter nor be expelled from the subarachnoid space, although minor fluctuations may be observed. Twelve experiments were performed. On occluding the external jugular veins, fluid was rapidly displaced from the subarachnoid space into the external system. This displacement of fluid lasted sometimes for one to three minutes. The volume of fluid displaced during this period averaged 1 c.c. It is interesting to recall that Mortensen and Weed found that an average introduction of 1·30 c.c. of saline into the subarachnoid space was necessary in order to double the pressure of the cerebrospinal fluid. The external volume remained constant after this initial displacement of fluid, save for minor fluctuations, in half the experiments. In the other half, fluid was steadily extruded into the external system. The maximum average rate of outflow observed in any one experiment was 0·023 c.c. per minute. Jugular occlusion was followed by a rise in the venous pressure in the torcular. The rise in pressure was, however, less than that observed when the escape of fluid from the subarachnoid space was prevented. This observation is in harmony with earlier findings (Bedford, 1936). In ten experiments the increase in the venous pressure averaged 150 mm. saline solution. The venous pressure was therefore rarely twice that of the cerebrospinal fluid. It was noted that, except for minor fluctuations, the venous pressure in the torcular usually remained steady throughout the experiment. It would appear, therefore, that the effect of jugular occlusion was to cause a rapid initial displacement of fluid from the subarachnoid space. This was followed in half the experiments by a steady extrusion of fluid which, however, never averaged more than 0·023 c.c. per minute. In the remaining experiments there was no evidence of inflow or of outflow of fluid and the external volume remained unchanged.

(3) *The rate of absorption of isotonic solution when the reservoir is set at a pressure level equal to twice that of the cerebrospinal fluid and the jugular veins are not ligated.*

Jugular ligation generally causes the pressure of the cerebrospinal fluid to be approximately doubled. It was decided to determine the rate of absorption of isotonic solution when the reservoir is set at a pressure twice that of the cerebrospinal fluid and the jugular veins are not occluded. Four experiments in all were performed. An average rate of absorption of 0·062 c.c. per minute was obtained. This figure is somewhat higher than that found by Mortensen and Weed, who obtained an average rate of absorption of 0·054 c c. per minute in thirteen experiments.

DISCUSSION.

The experiments on the effect of jugular occlusion on the absorption of isotonic solution when the reservoir is set at the pressure assumed by the cerebrospinal fluid would appear to indicate that (1) the return of the pressure of the cerebrospinal fluid to normal after ligation of the external jugular veins is brought about by a diminution of the total volume of the cerebrospinal fluid; (2) the fall in the venous pressure in the torcular is mainly dependent on the fall in the cerebrospinal fluid pressure. According to Weed and co-workers (1934, 1935-36) the cerebrospinal fluid is absorbed by a process of simple filtration through the arachnoid villi. Weed considers that "the total effective pressure activating the normal process of absorption of cerebrospinal fluid is compounded of the colloid osmotic pressure of the blood plus a hydrostatic factor derived from the difference in the subarachnoid pressure and the intracranial venous pressure." Weed (1935) states that the colloid osmotic pressure of the blood lies between 250 and 300 mm. saline solution. If these conclusions are correct, the absorption of the cerebrospinal fluid in the experiments under consideration may be expected to proceed at a markedly reduced rate in the most congested parts of the subarachnoid space. Jugular ligation generally causes the venous pressure in the torcular to equal or exceed slightly the pressure assumed by the cerebrospinal fluid. Normally the pressure of the cerebrospinal fluid is slightly higher than the venous pressure in the torcular. It would appear, however, from a consideration of the anatomy of the intracranial venous system of the dog (Bedford, 1934), that the venous pressure will probably be highest in the superior longitudinal, the straight and the lateral sinuses. In the remaining sinuses the pressure will be undisturbed or very slightly raised. Weed has shown that the cavernous sinus is particularly rich in arachnoid villi. In this region and in the subtentorial and spinal portion of the subarachnoid space, cerebrospinal fluid will be absorbed at a rate corresponding roughly with that observed when the pressure of the cerebrospinal fluid is doubled. The average rate of inflow in fifteen experiments was 0·049 c.c. per minute. This figure is slightly lower than that obtained when the pressure of the cerebrospinal fluid was doubled and the external jugular veins were not occluded. As already stated, however, a moderate fall in venous pressure occurred in a number of the experiments. This was invariably accompanied by an increased rate of inflow of fluid and is no doubt partly responsible for the relatively high figure. Nevertheless, it must be admitted that the rate of absorption in these experiments was greater than expected. The intracranial venous congestion involved the main areas in which absorption is generally supposed to take place. A more pronounced reduction in the rate of absorption was anticipated on the basis of Weed's theory of the absorption of cerebrospinal fluid. It is apparent that this aspect of the subject is in need of further study.

A diminution in volume of the cerebrospinal fluid may be brought about by a diminution in rate of production while the rate of absorption remains unchanged, or by an increased rate of absorption while the rate of production remains unchanged. It is also conceivable that a state of increased absorption may be accompanied by one of diminished production. We have as yet no precise knowledge concerning the effect of changes in the venous pressure on the formation of cerebrospinal fluid by the choroid plexuses. The results of the experiments on the effect of jugular occlusion on the absorption of isotonic solution when the pressure of the cerebrospinal fluid is maintained at its original level would appear to suggest that the raised venous pressure did not cause the production of cerebrospinal fluid to be diminished. It is, however, doubtful to what extent this conclusion is justifiable. The extrusion of fluid observed in half the experiments may have been caused in any of the following ways: (1) The reservoir may have been set at a lower pressure level than the true pressure of the cerebrospinal fluid. Stringent precautions were, however, taken to determine the normal level of the cerebrospinal fluid at the start of all experiments; (2) there may have been an increased production of cerebrospinal fluid; (3) the outflow of fluid may have been the result of a diminished rate of absorption into the venous sinuses; (4) the venous pressure in these experiments was raised suddenly, the resistance to vascular dilatation normally opposed by the raised pressure of the cerebrospinal fluid was almost entirely absent and fluid was displaced freely from the subarachnoid space. It is possible, therefore, that a condition of œdema and vascular dilatation was set up in the nervous system. The effect of rapid drainage of cerebrospinal fluid on the blood vessels of the central nervous system has been studied in detail by Masserman (1934, 1935). The outflow of fluid in the experiments under consideration may therefore have been caused in part by a spreading œdema and vascular dilatation of the central nervous system.

To sum up, it would appear that the return of the pressure of the cerebrospinal fluid to normal after ligation of the external jugular veins is caused by a diminution in volume of the cerebrospinal fluid. This decrease in volume of the cerebrospinal fluid may be brought about by an increased rate of absorption in those parts of the subarachnoid space which are least affected by the raised venous pressure. The fall in the venous pressure in the torcular would seem to depend mainly on the fall in the pressure of the cerebrospinal fluid.

SUMMARY.

An attempt has been made to discover the cause of the return of the pressure of the cerebrospinal fluid to normal after its artificial elevation by jugular occlusion. A study was made of the effect of jugular ligation on the absorption of isotonic solution from the subarachnoid space. It was concluded as a result of these experiments that (*a*) the return of the pressure of the cerebrospinal fluid to normal after jugular occlusion is due to a diminution in the volume of the cerebrospinal fluid; (*b*) this diminution in volume may be brought about by increased absorption in those parts of the subarachnoid space which are least influenced by the raised venous pressure; (*c*) the accompanying fall in the venous pressure in the torcular is mainly dependent on the fall in the pressure of the cerebrospinal fluid.

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VASCULAR LESIONS IN THE BRAIN-STEM AND OCCIPITAL LOBE OCCURRING IN ASSOCIATION WITH BRAIN TUMOURS.[1]

BY MATTHEW T. MOORE (PHILADELPHIA) AND KARL STERN (LONDON).

THE study of vascular lesions occurring in brains which are the seat of tumours, using this word in the broad sense of space-taking lesions, is important from several points of view. Firstly, their appearance complicates the clinical picture and produces difficulties in diagnosis. Secondly, an investigation of their pathogenesis may assist in the general problem of intracranial circulation in relationship to lesions producing increased intracranial pressure.

Hæmorrhages in the lower brain-stem were first studied in connection with traumatic cerebral lesions. Duret (1919-20) described multiple small hæmorrhages in the region of the aqueduct and the floor of the 4th ventricle, which he thought were produced by a sudden increase in the local cerebrospinal pressure. In some instances these lesions appear some time after the original cerebral trauma (" Spät apoplexie "—Bollinger). Kolisko (1911) abandoned Duret's explanation of the pathogenesis of the hæmorrhagic lesions and advanced the theory of the greater vulnerability of the basilar artery and its branches from a mechanical point of view. The earliest comprehensive survey of the problem of brain-stem hæmorrhage, was made by Attwater (1911) from cases of cerebral apoplexy and trauma. In 67 cases he found an accompanying pontine hæmorrhage in 30 per cent., mostly in cases where the cerebral hæmorrhage was large and had ruptured into the ventricle. He expressed the opinion that the pontine hæmorrhage was secondary to the cerebral hæmorrhage. In one case, however, where there was a large pontine hæmorrhage and a small hæmorrhage in the internal capsule, he felt that the pontine hæmorrhage was the primary one.

In a special study of spontaneous multiple cerebral hæmorrhages, Greenacre (1917) found the combination of a cerebral and pontine hæmorrhage in 63 per cent. of cases studied. She suggested that in these cases a " friction " must occur between the two channel beds, the carotid and the vertebral, and, "since the meeting takes place in the posterior part of the system, owing to the greater length and more circuitous route of the vertebrals, the pressure throughout the basilar is presumably increased above that in the other arteries, and its branches are subjected to unusual strain."

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[1] From the Pathological Laboratory, National Hospital, Queen Square.

Wilson and Winkelman (1926) recorded a comparative study of 13 cases of pontine hæmorrhages occurring in 129 autopsies, which included 26 cases of trauma, 40 of vascular disease, 52 of neoplasm and 11 of abscess. Of the 13 cases of pontine hæmorrhages only 4 were associated with the lesions we are here concerned with, namely 3 neoplasms and 1 abscess. Their explanation of the causative factors, like that of Kolisko, was that the increased intracranial pressure pushed the pons against the base of the skull. They also suggested that "in the traumatic cases it is probable that the upper pons transmits the impact from one hemisphere to the other, and thus may be injured indirectly."

In a series of sixteen cases of brain tumour, Rosenhagen (1932) found ten (62·5 per cent.) in which multiple pontine and tegmental hæmorrhages occurred. He regarded these hæmorrhages as analogous with the hæmorrhages occurring in trauma and as due to sudden changes in cerebrospinal fluid pressure. He ascribed the situation of these hæmorrhages to the exposed position of the basilar artery.

The problem also was taken up by Bannwarth (1935). He found hæmorrhage in 4 temporal and 1 frontal lobe tumours, and taking into account Rosenhagen's 6 temporal, 2 parietal, 1 hemispheric, and 1 frontal lobe tumours, concluded that temporal lobe tumours have a greater tendency than others to produce these lesions. In his cases no causal relationship with operation could be shown, as only one case had been operated upon. In explanation he adopts the general theory of Albert, viz., as the blood-pressure falls gradually from the arteries to the capillaries and from these to the veins the rising intracranial pressure must act first on the veins as the point of least resistance. If the intracranial pressure rises sufficiently to compress the veins while the arterial flow is still maintained, congestive arterial hyperæmia, excessive engorgement of the capillaries, and, finally, arterial hæmorrhage by diapedesis and by rhexis must occur. If acute brain swelling occurs in tumours the resulting increased-pressure first acts upon the region offering least resistance, i.e. the foramen magnum and the lower brain-stem, compressing the veins in that area and producing arterial congestive hyperæmia and hæmorrhage in the described way.

Stern (1933) pointed out that in diseases with increased intracranial pressure other than tumours, e.g. cerebral injury, renal disease, and heatstroke, the arteries in the posterior fossa seem to be exposed to an unusual strain and are more liable to disturbances than the arteries in other areas of the brain. In a case of heat-stroke he described symmetrical softenings in the lower brain-stem and hypothalamus, in both occipital poles and in the left hippocampus. There was a separation of the intimal layer of the extracerebral arteries supplying these areas and blood was found between the intima and media. Apparently this had happened in previously healthy arteries. Finally, Adolf Meyer (1920), in his paper on "Herniation of the Brain," described one case of cerebral tumour in which compression of the posterior cerebral artery had caused an infarction of the occipital lobe.

Material and method.—One hundred and thirty brains in which brain tumour or abscess was present were examined for evidences of vascular lesions. Of these the first hundred were from a consecutive series of autopsies, and 14, or 14 per cent., showed accompanying vascular lesions either in the pons, mid-brain or occipital lobe. In addition to these 14 cases, 4 showing vascular lesions were examined among the remaining 30 brains of the entire group. Five of the total of 18 cases of hæmorrhage cases presented the gross appearance of occipital lobe infarction. Fourteen cases were studied histologically in frozen and celloidin sections with Nissl, Hæmatoxylin-Van Gieson and Herxheimer-Sharlach R stains. The basilar artery and its branches and the posterior cerebral and its calcarine branches were dissected out, embedded in paraffin and studied with Hæmatoxylin-Van Gieson and Weigert's Elastica stains.

To Dr. J. Godwin Greenfield we are indebted for the privilege of using this material and for his autopsy reports, and to the honorary physicians of the National Hospital, Queen Square, for permission to review the following case reports.

Calcarine Infarction.

Case 1.—E. B. (Case No. 67/37), female, aged 43 (Dr. Gordon Holmes), was admitted to hospital on March 1, 1937, complaining of weakness of the left arm and left leg. She had enjoyed her usual health until one week before entering hospital. On February 25, 1937, she yawned the greater part of the afternoon and was very drowsy. She had difficulty with her speech, and found her left arm weak. On February 27 her left arm had become useless and she noticed that she was dragging the left leg. There was no pain or headache associated with these symptoms.

The past medical history and family history were irrelevant.

Examination.—She showed a definite organic dementia and marked stammer and was unable to carry out elementary mathematical problems. There was no evidence of field defect and the optic discs were normal. The pupils were irregular and unequal in size, completely inactive to light but reacted well on convergence. There was marked bilateral ptosis. There was hypalgesia on the nose and cheek, more pronounced on the right side. The corneal reflex was more active on the right than on the left. She showed left lower facial weakness. The other cranial nerves were normal. There was definite left hemiparesis, more pronounced in the upper limb and accompanied with a moderate degree of hypertonus. There was a slight hypalgesia over the thorax and inner border of the upper limbs.

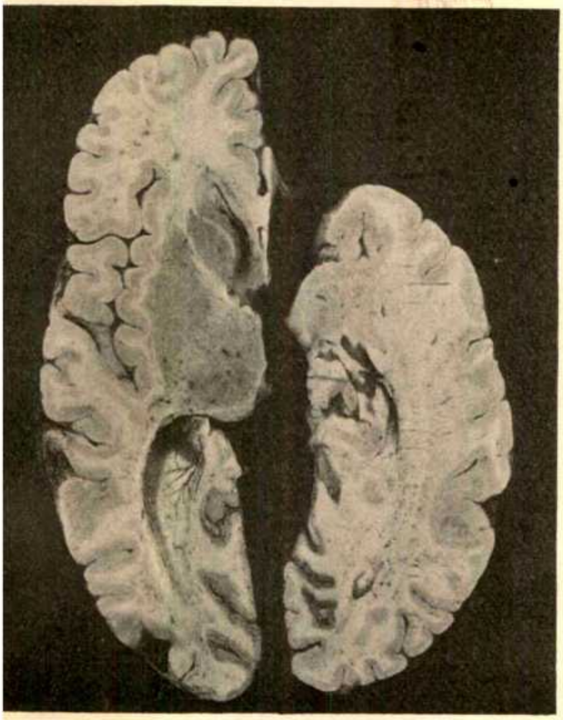

FIG. 1.

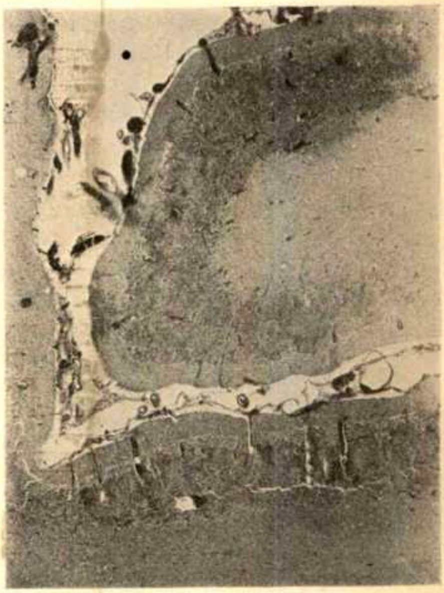

FIG. 2.

FIG. 1.—*Case* 1. Bilateral infarction of the calcarine cortex in a case of tumour of the right basal ganglia.

FIG. 2.—*Case* 1. Laminar softening of the cortex. There is a clear demarcation between the first two layers which are fairly well preserved and the remaining layers which bear the brunt of the softening. (Cresyl violet—low power.)

On March 2, 1937, lumbar puncture gave a clear cerebrospinal fluid under 120 mm. water pressure. There were no cells, total protein was 0·18 per cent. During the patient's stay in hospital her mental and neurological abnormalities became more marked. On March 30, she showed a paresis of conjugate movements of the eyes upwards. Slight papillœdema first appeared on April 11 but was not definite until May 6. She had periods of unconsciousness from May 16 to the time of her death on June 12, 1937.

Post-mortem examination.—The examination of the viscera was negative.

Brain: The arteries were healthy. There was no swelling of the pons, mid-brain or convolutions. On examining the thalamus on the two sides after incision of the corpus callosum, that on the right was definitely bulkier than that on the left. On incision here a rounded mass of tumour with ill-defined edges was seen just under the ventricular surface of the thalamus, and this was found to extend downwards into the right side of the mid-brain.

In the *calcarine region*, on both sides, the cortex was shrunken, soft, and of reddish-brown colour. The change was not limited to the area striata only but also extended to the area parastriata. The cortical involvement on the left side was more extensive than on the right (fig. 1). However, in some cross sections the lesions appeared almost symmetrical. The white matter adjacent to the involved area was somewhat soft and shrunken but did not show any abnormal colour. The vessels supplying the areas described appeared quite normal macroscopically.

Histological examination.—In the right occipital cortex (areæ striata and parastriata) the ganglion cells of several gyri had entirely disappeared and had been replaced by a glial proliferation and new vessel formation. The first two cortical layers appeared fairly well preserved but the remaining layers were severely involved (fig. 2). There was considerable proliferation of glial elements, consisting of macroglia and "gemästete" glia. In addition, there was an extensive capillary proliferation, segregation of capillary endothelium, and "gitter" cell formation; the white matter only showed a slight diffuse glial reaction. The left occipital cortex presented the same histological appearance. The pial vessels in the areas studied were normal. The dissected isolated occipital and pontine vessels were normal histologically.

Calcarine Infarction.

Case 2.—A. S. (Case No. 39/35), male, aged 44 (Dr. James Collier), was admitted to hospital on February 21, 1935, complaining of headaches and confusion in speaking. In September of 1934, during an attack of influenza, he noticed that his memory was poor. Since that time he had persistent headache, chiefly in the evening. During October, 1934, he developed difficulty in writing and speaking. He lost interest in his family and his business.

Examination.—The patient was emaciated. There was a difficulty in speech and his attention was poorly sustained. The nasal halves of both discs were blurred, but no definite swelling was visible. There was slight bilateral ptosis. Movement of the right upper lip was somewhat weak. The other cranial nerves were normal. Motor function and sensation could not be properly evaluated because of lack of co-operation. The reflexes showed no abnormal responses. The blood-pressure was 130 systolic, 90 diastolic. The blood-count was normal.

A ventricular puncture performed February 26, 1935, showed the following: Initial pressure 300 ++ mm. water, clear, colourless fluid, 4 cells, total protein 0·08 per cent., Nonne-Appelt +, Pandy +, Lange negative.

Post-mortem examination.—Brain only examined. The skull was thinned showing convolutional markings. This was more marked in the region of the left parietal eminence where the inner aspect of the bone was redder and rougher than on the right, and the middle meningeal furrow was obliterated. The left temporal lobe was attached to the dura over the outer aspect of the pole, and here a large firm tumour was found coming to the surface. There was a yellowish degeneration in its mesial aspect.

There was considerable absorption of the bone in both middle cranial fossæ, especially the left. The floor of the sella was a very thin shell of bone and the posterior clinoid processes were almost completely destroyed.

Examination of the brain after fixation showed a very marked herniation of the left uncus through the incisura tentorii, and a fairly deep notch with underlying bruising was found on the outer surface of the right crus.

At the margin of the *left calcarine fissure* the cortex was thinned, was reddish in colour, and appeared to be softer than normal. The pons and mid-brain showed no change.

Histological examination.—In the affected calcarine area no nerve-cells could be seen, but the glia cells, especially microglia, were swollen and increased in number. The vessels were proliferated and the capillary wall elements were also swollen. There was considerable "gitter" cell formation.

The extracerebral vessels, both arteries and veins, in the involved area appeared normal.

Calcarine Infarction and Pontine Hæmorrhage.

Case 3.—A. H. (Case No. 47/34), male, aged 31 (Dr. C. P. Symonds), was admitted to hospital on April 4, 1934, complaining of pains in the eyes and headache. These complaints had been present for four months. For one and a half years he had had pains over the front of the left side of his chest. There had been tingling in the legs for a few days. He had had one attack of vomiting three weeks before admission.

Examination.—There was a bilateral papillœdema of three to four dioptres. The remaining cranial nerves were normal. The reflex activity showed no gross abnormalities. The gait was unsteady. All forms of sensation were normal. The blood-pressure was 150 systolic, 80 diastolic.

Lumbar puncture performed April 9, 1934, showed an initial pressure of 300 + mm. water. The cerebrospinal fluid was normal. The patient had severe headache following the puncture, but then remained fairly well until April 12, when he could not be roused. The corneal reflexes became very sluggish, and the pupils were fixed to light stimulation. The pulse dropped from 64 to 52. 100 c.c. of 50 per cent. glucose administered intravenously produced no improvement. The right lateral ventricle was tapped in the ward on April 12 and 100 c.c. of cerebrospinal fluid removed. The ventricular fluid was normal. The patient remained unconscious. A posterior fossa decompression was performed under general anæsthesia. The dura was not under abnormal tension and on opening the dura the cisterna magna was considerably distended with cerebrospinal fluid. There was no herniation of the cerebellar tonsils. The patient died on the day of operation.

Post-mortem examination.—Only the brain examined. There was a recent posterior fossa decompression and burr holes for ventriculography were present in the parieto-occipital regions. The convolutional markings on the inner surface of the skull were pronounced. The floor of the sella turcica was membranous. The middle cranial fossæ and the lesser wings of the sphenoids on both sides were considerably eroded by pressure.

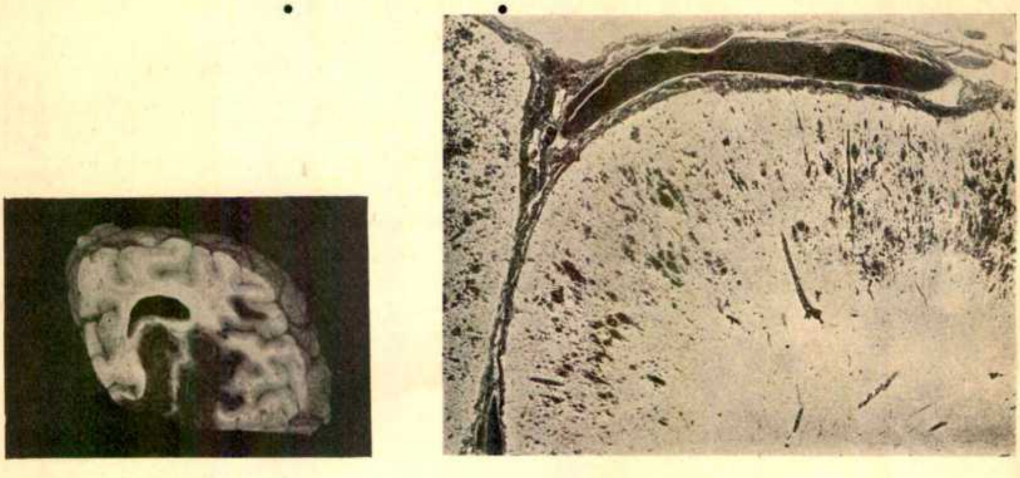

FIG. 3.—*Case* 3. A. Hæmorrhagic infarction of the visual cortex. B. Necrosis and capillary hæmorrhages confined almost exclusively to the cortical grey matter. (Hæmatoxylin Van Gieson—low power.)

Both occipital lobes were very congested and soft in the inner and inferior surfaces. The condition was one of acute massive hæmorrhagic infarction (fig. 3A). On opening the lateral ventricles there was a bilateral hydrocephalus, and on removing the fornix a pale-green ball-like tumour was found attached slightly to the tela chorioidea and lying over the iter of Sylvius.

In the areæ parastriata and striata areas the cortex was somewhat soft and reddish brown in colour, this state being limited to the grey matter only and not extending into the subcortex. On the left side a small area of the posterior portion of the temporal lobe was similarly involved. The posterior cerebral artery, on macroscopical examination, appeared normal on both sides.

In the tegmental part of the pons extending up to the caudal third of the red nucleus there were multiple hæmorrhages in the distribution of the central arteries.

Histological examination.—The tumour was a colloid ball tumour (paraphysial cyst). The pontine hæmorrhages were composed of many small single hæmorrhages. The nerve-cells in the hæmorrhagic areas had undergone severe cell change. There was no glial or mesodermal reaction in the vicinity of the hæmorrhages. In the sections examined there was no evidence of rupture of the vessels. In a section from the right area parastriata the cortex showed multiple capillary hæmorrhages throughout its extent in two opposite gyri (fig. 3B). The nerve-cells in the affected area showed hyperchromatic nuclei and impregnation with formol pigment (hæmatin). The capillaries in the centres of the small hæmorrhages did not show endothelial cells with nuclei, but were represented by indistinct shadows of formol pigment, or showed an entirely amorphous structure. There was no glial or mesodermal reaction. The superficial layers showed much less hæmorrhage than the remaining part of the cortex.

The extracerebral arteries and veins of the area examined appeared normal.

Calcarine Infarction and Mid-brain Hæmorrhage.

Case 4.—A. C. (Case No. 109/35), male, aged 49 (Dr. George Riddoch), was admitted to hospital on December 12, 1935, complaining of continuous headache and frequent vomiting. One month before admission he had a sudden severe headache in the middle of the night which lasted fifteen minutes. It recurred the next night and the following day, and was then accompanied by vomiting. He also had tremor of the right hand and disturbance of taste. He lapsed into a deep coma on the day of admission. He vomited while comatose.

Examination.—The patient was deeply comatose and had stertorous respiration. The vomit contained coffee-ground material. The pulse-rate was 58. Both fundi showed papillœdema with retinal hæmorrhages. The swelling was four to five dioptres in each disc. There was bilateral ptosis. The corneal reflexes were absent. The left corner of the mouth was lower than the right. The remaining cranial nerves could not be tested properly. The limbs were flaccid and motionless, and the reflexes abolished. Sensation could not be tested.

On the day of admission an emergency ventricular tap was performed. The ventricular pressure was 330 mm. water pressure. The fluid from the left ventricle was clear and contained no cells, the total protein was 0·3 per cent. On the right side yellow fluid was obtained from a temporal cyst. The patient died the following day without having regained consciousness.

Post-mortem examination.—The skull was generally thin, especially both middle cranial fossæ, the right more than the left. The dura was very tense.

A soft cystic tumour occupied the inner part of the right temporal lobe, including the hippocampal gyrus and the uncus. The outer convolutions were quite flattened and very soft.

Multiple, diffuse hæmorrhages were present in the dorsal part of the mid-brain.

There was a hæmorrhage the size of an olive above the right lateral ventricle in the subcortical white matter of the superior portion of the caudal level of the parietal lobe. The walls of the hæmorrhagic cavity were smooth, and the clot was adherent only in a very small part.

The calcarine fissure and the adjacent areas of the cortex of the right occipital lobe were evenly shrunken and softened, and were of a greyish-brown colour with stippled reddish-brown areas. This change did not involve the subcortical white matter. The entire lesion extended from the parieto-occipital sulcus to the tip of the occipital pole. The left occipital lobe (macroscopically) was intact. The basilar and both posterial cerebral arteries showed no macroscopical changes.

Histological examination.—The tumour is a glioblastoma. In the right areæ striata and parastriata there are multiple capillary hæmorrhages throughout the grey matter. The capillaries show amorphous walls or have disintegrated. In some areas within the affected zone they are only extremely congested. The nerve cells in the same area show ischæmic and homogeneous cell change and are impregnated with formalin pigment (hæmatin). There is no glial or mesodermal reaction.

The extracerebral vessels are hyperæmic and show formalin pigment in fine dust-like granules in their wall.

The left occipital cortex shows a similar change but to a lesser degree.

Calcarine Softening.

Case 5.—C. P. (Case No. 72/33), female, aged 47 (Dr. F. M. R. Walshe), was admitted to hospital on September 26, 1933. She gave a history of headaches over a period of three years. There was trembling of the right hand eighteen months previous to admission, and an acute spastic paraplegia with loss of power of the legs thirteen months before entering hospital. The paraplegia lasted a fortnight, but cleared up completely. For several weeks before entering hospital she had severe headaches, numbness of the left side of the body, vomiting, loss of memory and failing vision.

Examination.—She manifested difficulty in understanding written words and her memory was very defective. There was a complete right homonymous hemianopia. The discs edges were blurred. There was numbness of the left side of the face. The tendon reflexes were more active on the right than on the left, and the right plantar response was in flexion whereas the left was in extension.

Lumbar puncture performed September 27 showed cerebrospinal fluid under a pressure of 275 mm. water, and containing a total protein of 0·175 per cent.

A right parietal decompression was performed October 10, 1933. The patient died on the following day.

Post-mortem examination.—There was a marked herniation of the uncus on the left side through the incisura tentorii, and a well marked notch was present on the right crus at the junction of the pons and mid-brain. There was a well-marked cerebellar pressure cone. A firm tumour adherent to the dura was found in the region of the left marginal gyrus. There was an area of cortical softening affecting the territory supplied by the left posterior cerebral artery. This included the whole of the calcarine region and surrounding parts of the cortex (fig. 4).

The spinal cord was normal.

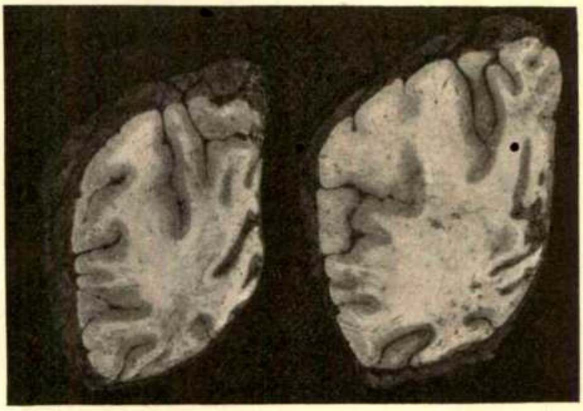

FIG. 4.—*Case* 5. Unilateral softening and shrinkage of the visual cortex.

Histological examination.—The tumour is an endothelioma. The affected cortical area shows a marked "gitter" cell formation in the lower cortical layers. The first two layers are better preserved. In Scharlach R preparations the gitter cells which are strictly confined to the grey substance contain bright red-staining substances.

The extracerebral vessels are normal.

Softening in Mid-brain.

Case 6.—W. G. (Case No. 48/37), male, aged 67 (Dr. Gordon Holmes), was admitted to hospital on April 5th, 1937, complaining of weakness, failure of memory, speech difficulty, drowsiness, restlessness and headaches. During February, 1937, the patient was taken ill with influenza, following which he remained quite weak, had persistent light-headedness, spoke in a silly fashion at times, had difficulty in reading and writing and developed headache and periodic attacks of drowsiness. The day before admission his drowsiness was interrupted by accesses of great violence and his speech was unintelligible.

Examination.—The patient was conscious, but was unable to give any information because of a severe dysphasia. He did not understand simple commands, and he was unable to write or name common objects. The discs were normal. There was disinclination to move the eyes to the right. The pupils were irregular and the light response was diminished. There was some hypalgesia on the right half of the face. The right lower half of the face showed a marked weakness. The other cranial nerves could not be properly examined There was a mild right hemiparesis. The heart was moderately enlarged to the left. The blood-pressure was 170 systolic, 120 diastolic.

Lumbar puncture performed on April 12, 1937, showed the cerebrospinal fluid under a pressure of 300 + mm. water. The fluid was yellow, containing 25 cells, total protein 0·4 per cent., Nonne Appelt + +, Pandy + + +, Lange and Wassermann negative. During the stay in hospital the patient deteriorated steadily. On April 13 an exploratory puncture of the left temporal lobe was made. The patient died on May 1, 1937.

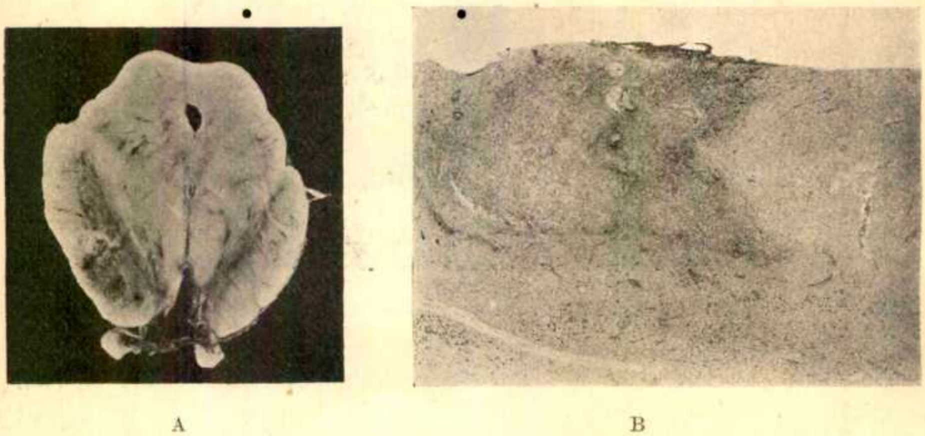

Fig. 5.—*Case* 6. A. Softening in the mid-brain. B. Low power view of A. (Cresyl violet.)

Post-mortem examination.—Only the brain examined. The dura was moderately tense. There was no evidence of a cerebellar pressure cone. A brownish tumour mass was exposed filling the left optic thalamus and projecting into the 3rd ventricle. The tumour extended from the rostral end of the left thalamus to the posterior tip of the posterior horn of the lateral ventricle. It involved the basal ganglia and their surrounding structures and showed a partial gelatinous degeneration.

There was a greyish soft area in the mid-brain which extended from the medial 3rd of the peduncle along the substantia nigra up to the level of the oculo-motor nucleus (fig. 5A). The pons and the cortex of the occipital lobes appeared normal. The basilar artery and the posterior cerebral arteries were macroscopically normal.

Histological examination.—The affected area in the pes pedunculi shows a softening in a rather early stage with an extensive glial reaction, formation of plump glial cells, capillary proliferation, but with few gitter cells yet developed (fig. 5B). The ganglion cells of the substantia nigra are unaffected in the marginal zone of the area. The extracerebral vessels are normal.

Hæmorrhages in the Mid-brain and Pons.

Case 7.—L. J. (Case No. 31/37), male, aged 44 (Dr. C. P. Symonds), was admitted to hospital on March 23, 1937. His symptoms appeared in January, 1937, with convulsive seizures. Following this he progressively developed speech difficulty, drowsiness, emotional changes, and six days before admission a left homonymous hemianopia. The patient was left handed.

Examination.—Both optic discs showed blurred edges and the retinal veins were engorged. There was a divergent strabismus and the pupils were fixed to light. There was left facial weakness and left hemiparesis of the limbs with increased reflex activity.

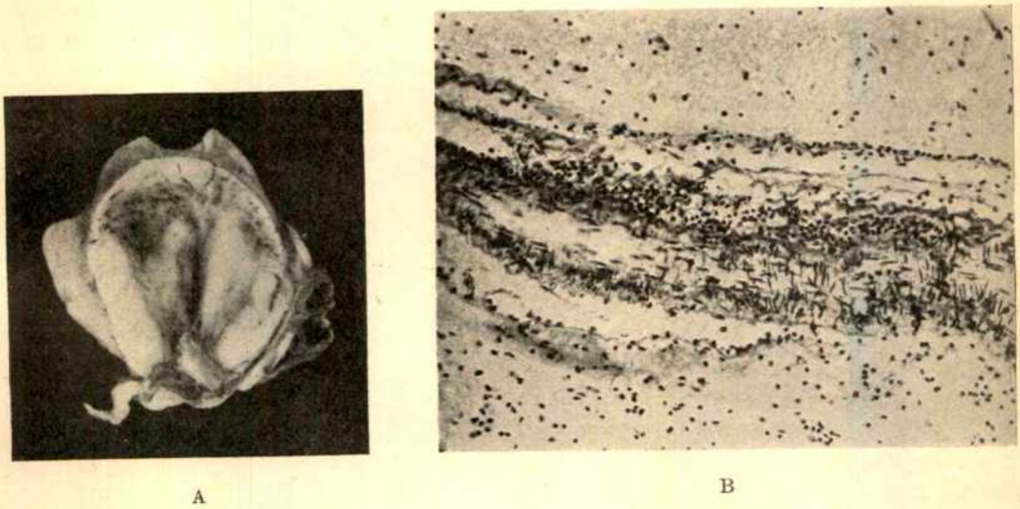

FIG. 6.—*Case* 7. A. "Fountain-like" hæmorrhage in the mid-brain. B. Arteriole showing distension and partial dissection of the coats, subadventitial hæmorrhage, and marginal position and beginning emigration of the leukocytes.

On March 23, 1937, exploratory craniotomy revealed a right temporal lobe cyst. The patient died on the following day.

Post-mortem examination: There was no evidence of cerebellar or temporal lobe herniation. A soft brownish hæmorrhagic tumour mass involved the right temporal lobe, extending from the tip of the lobe well into the occipital lobe. A hæmorrhage, external to and below the posterior horn of the ventricle, formed the most backward portion of the mass. This hæmorrhage appeared to be fresh. There were two hæmorrhagic areas in the mid-brain, one lying mesially near the caudal end of the red nucleus, the other being on the right side lateral to the central grey matter of the aqueduct. Both were surrounded by numerous punctate hæmorrhages. The tegmentum of the pons was also involved with numerous punctate hæmorrhages (fig. 6A). The basilar artery appeared normal.

Histological examination.—The tumour is a large-celled astrocytoma. The hæmorrhagic area in the mid-brain consists of many single hæmorrhages most of which show clearly their relationship to vessels. There are peri-adventitial hæmorrhages around arterioles extending into the surrounding tissue. The walls of the arterioles show all degrees of necrotic change. In some hæmorrhagic areas only the shadows of arterioles are to be seen in the centre. In some of these vessels the adventitia is to be seen in a disintegrating state and the hæmorrhage extending though the sub-adventitial into the peri-adventitial space. The leucocytes show a marginal arrangement in these vessels (fig. 6B). The capillaries are distended. The extracerebral vessels are dilated and full of blood, but apart from this are normal. There is no reaction of glial or mesodermal cells in the area of the hæmorrhage.

Hæmorrhages in the Mid-brain and Pons.

Case 8.—S. L. (Case No. 109/36), male, aged 45 (Dr. Gordon Holmes), admitted to hospital November 28, 1936. The patient contracted a septic infection of the left little finger in September, 1936, following which he developed convulsive seizures, headaches, vomiting, giddiness, forgetfulness, speech disorder, and visual disturbance.

Examination.—The following positive signs were found: general mental impairment, drowsiness, blurring of both optic discs and congestion of retinal veins, right corneal reflex sluggish, left lower facial weakness, weakness of left arm, abdominal reflexes absent bilaterally, extensor plantar reflex on the left side, slight loss of postural sense in left fingers and toes.

A transitory state of coma existed on the day after admission. During this coma the pulse was 70 and the blood-pressure 100 systolic, 70 diastolic. He regained consciousness, and on December 8, 1936, he again lapsed into coma and died the same day.

Post-mortem examination.—The dural sinuses were normal. There was a slight cerebellar pressure cone and a very marked herniation of both temporal lobes through the incisura tentorii, especially on the right side. On the right side, in addition, the anterior part of the lingual gyrus was purplish and showed small hæmorrhages. The right hemisphere was herniated under the falx cerebri.

There was a thin-walled abscess in the inferior portion of the right parietal lobe. The pons showed hæmorrhages in several areas, the largest being in the centre, and several small ones in the periphery (fig. 7). In the mid-brain there were many small hæmorrhagic areas at the level of the caudal end of the red nucleus. Some of these were symmetrically situated between the red nuclei. The basal vessels appeared normal.

Histological examination.—A section (Nissl) from the area of the left herniated uncus shows a normal histological appearance of Ammons horn and the adjoining temporal gyri.

The pontine hæmorrhages show some tendency to spread in the direction of the surrounding myelin fibre network. These areas contain necrotic ganglion cells with marked incrustation of formalin pigment. There is no tissue reaction around the hæmorrhages. The extracerebral vessels appear normal.

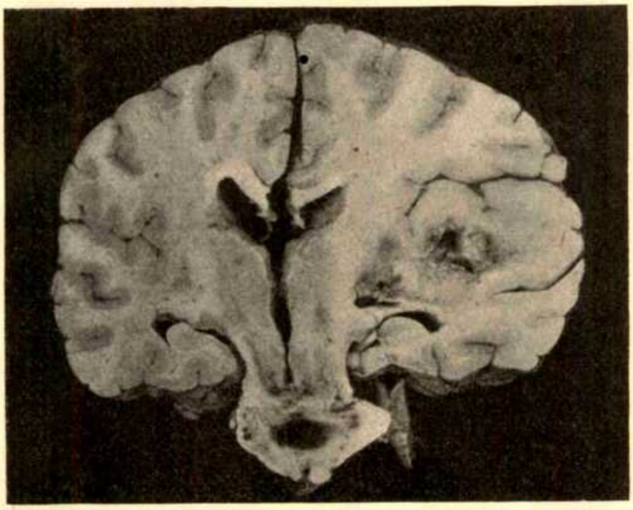

FIG. 7.—*Case* 8. Right parietal lobe abscess and central pontine hæmorrhage.

Pontine Hæmorrhage.

Case 9.—J. G. (Case No. 102/36), male, aged 58 (Dr. C. P. Symonds), was admitted to hospital on October 24, 1936. He had complained of frontal headache for one year and dizziness for six months preceding admission. There was a progressive deterioration in speech and strength for two months, and he began to have attacks of vomiting one month before coming to hospital.

Examination.—He showed a rather severe aphasia, a tendency to perseveration, and was unable to write despite being able to form letters. There was complete alexia. The edges of both discs were blurred and the retinal veins were full. Nystagmus was present, more marked on the right. There was a slight right lower facial weakness. The posture in the right arm was poorly maintained and he balanced insecurely on the right leg. The blood-pressure was 120 systolic, 85 diastolic.

Lumbar puncture on October 25, 1936, revealed a pressure of 165 mm.

water. The cerebrospinal fluid was slightly yellow and contained 14 cells to the cubic millimetre. The total protein was 0·22 per cent.

The patient died on November 12, 1936.

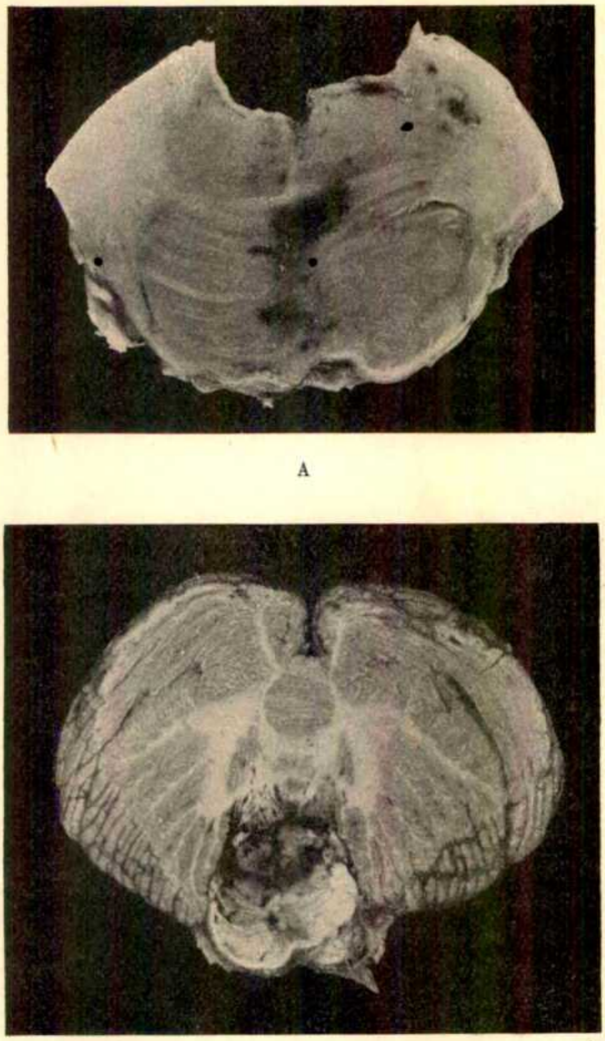

FIG. 8.—*Case* 9. Multiple pontine hæmorrhages at different levels (A, B).

Post-mortem examination.—The dura was very tense. There was no cerebellar pressure cone. The inner part of the left temporal lobe was herniated through the incisura tentorii. The crus on the right side was bruised fairly deeply and tore when the brain was turned over.

There was a tumour in the left middle temporal gyrus at the posterior end of the fissure of Sylvius. On section it extended inward and upward as a yellow degenerated mass.

The ventral part of the pons and most of the tegmentum (fig. 8A) was ploughed up by hæmorrhages. In the caudal 3rd of the pons the hæmorrhage appeared to be limited to the central core of the pons (fig. 8B).

The neighbourhood of the tip of the posterior horn of the right lateral ventricle was of a softened consistency. There was no evident disease of the blood-vessels.

Histological examination.—The tumour is a glioblastoma.

In a section from the pons (cresyl-violet), there are hæmorrhages in several layers, some of which show a small necrotic vessel in the centre. The ganglion cells in the hæmorrhagic area show severe cell change and are impregnated with formalin pigment. There is no mesodermal or glial reaction in the affected areas. The right cerebral cortex is normal histologically. The extracerebral vessels are normal.

Pontine Hæmorrhage.

Case 10.—F. H. (Case No. 74/36), female, aged 60 (Dr. G. Stewart), was admitted to hospital on August 18, 1936. She gave a history of convulsive seizures over a period of three years, weakness of the right leg, and later of the right arm, mental impairment and speech difficulty.

Examination.—She showed the following signs: A disturbance of speech comprehension, writing and memory; slight blurring and hyperæmia of the optic discs; right homonymous hemianopia, and right spastic hemiparesis.

A lumbar puncture performed on August 20, 1936, showed a pressure of 190 mm. water, clear, colourless cerebrospinal fluid, which contained no cells and a total protein of 0·09 per cent. The patient died on September 5, 1936.

Post-mortem examination.—There was a left frontal vertical endothelioma. The base of the sella was thinned, and the sphenoidal sinus contained some pus. The tumour lay immediately in front of the fissure of Rolando, sparing the paracentral lobule, and reaching half-way downwards to the Sylvian fissure.

There a was central hæmorrhage in the tegmental part of the pons which extended up to the level of the red nucleus. There were also small hæmorrhages in the peripheral areas of the pons. The rostral part of the central pontine hæmorrhage corresponded to the vascular distribution of the caudal twigs of the retromammillary (Foix-Hillemand) branches of the posterior cerebral arteries (figs. 9A, 9B, 9C). The basal vessels showed no changes macroscopically.

Histological examination.—The tumour is an endothelioma of very fibrous type. The section of the involved area shows a large hæmorrhage surrounded by a zone of vascular congestion. At another level not far distant from the main focus of hæmorrhage, the vessels are surrounded by a peri-adventitial hæmorrhage. The branches of the retromammillary vascular bundle are congested but show no mural change. At a level more caudal to the area of the hæmorrhage, the basilar artery shows intimal proliferation of a mild degree.

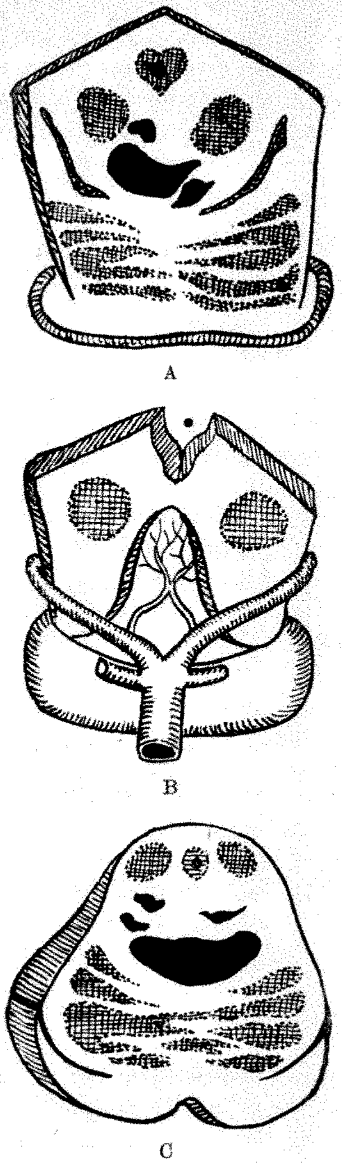

FIG. 9.—*Case* 10. Multiple central hæmorrhages in the mid-brain corresponding to the caudal branches of the retromammillary arterial bundle (B).

Hæmorrhages in Mid-brain and Pons.

Case 11.—C. C. (Case No. 98/35), female, aged 38 (Dr. F. M. R. Walshe), was admitted to hospital on October 31, 1935. There was a history of severe intermittent headaches since April, 1935, with periods of drowsiness and speech difficulties.

Examination.—There was a definite aphasia; blurring of both optic discs; right lower facial weakness, right hemiplegia; hypalgesia of the right side of the body; incontinence of urine. Lumbar puncture performed on November 9, 1935, showed a pressure of 300 mm. water. The cerebrospinal fluid was slightly yellow, contained 8 cells to the cubic millimetre, total protein 0·04 per cent. For twenty-four hours preceding death she was stuporous and the temperature was slightly elevated. She died on November 10, 1935.

Post-mortem examination.—The dura was tense and the convolutions were flattened in both hemispheres. There was no cerebellar pressure cone. A left temporal lobe tumour was found which extended into and involved the left frontal lobe, the 3rd ventricle, the right optic thalamus and the optic chiasma and optic nerves. The ventricular portion of the tumour was hæmorrhagic. (Only the left half of the brain and brain-stem was available for examination.)

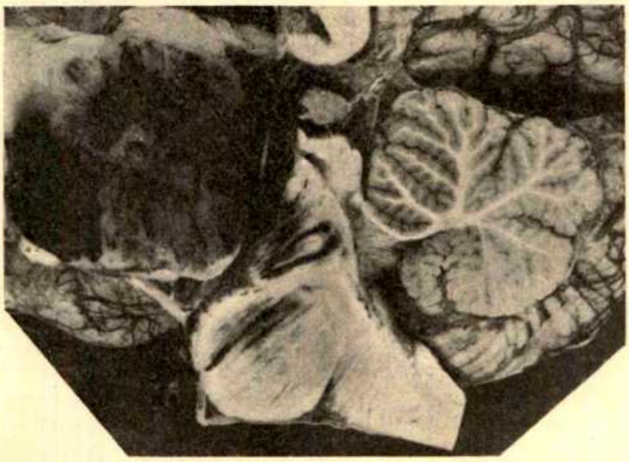

FIG. 10.—*Case* 11. Basal portion of the tumour, and pontine hæmorrhages from the central ascending branches of the basilar artery.

Several of the long central arteries of the pons and mid-brain showed peri-arterial hæmorrhages along their entire course (fig. 10). The substantia nigra showed greyish discoloration and engorged vessels. The basilar artery showed no pathological change.

Histological examination.—The tumour is a glioblastoma.

A section at the rostral level of the left half of the mid-brain, shows peri-adventitial hæmorrhages around some of the central ascending arteries. The ganglion cells in this area are intact. There is no tissue reaction. The extracerebral vessels in the interpeduncular fossa are extremely dilated but otherwise normal.

Hæmorrhages in Mid-brain.

Case 12.—A. C. (Case No. 85/35), male, aged 55 (Dr. Gordon Holmes), was admitted to hospital in a comatose state on September 28, 1935. Headaches began gradually about one month before admission. There was a history of a convulsive seizure and of speech difficulties which began after the onset of headache. For a fortnight previous to admission the patient showed drowsiness alternating with restlessness, incontinence of urine, mumbling speech and finally coma. He had been a heavy drinker for many years.

Examination.—The patient was comatose and cyanotic, and had Cheyne-Stokes' breathing. There was a blurring and hyperæmia of both optic discs, the pupils were equal in size, dilated and fixed to light, there was a spastic paralysis of the arms and legs, and bilateral plantar extensor responses. Lumbar puncture performed on September 28 showed a slightly blood-stained cerebrospinal fluid under a pressure of 5 mm. Three c.c. were removed and 30 c.c. of normal saline injected. The pulse became stronger, but soon thereafter weakened and the patient died.

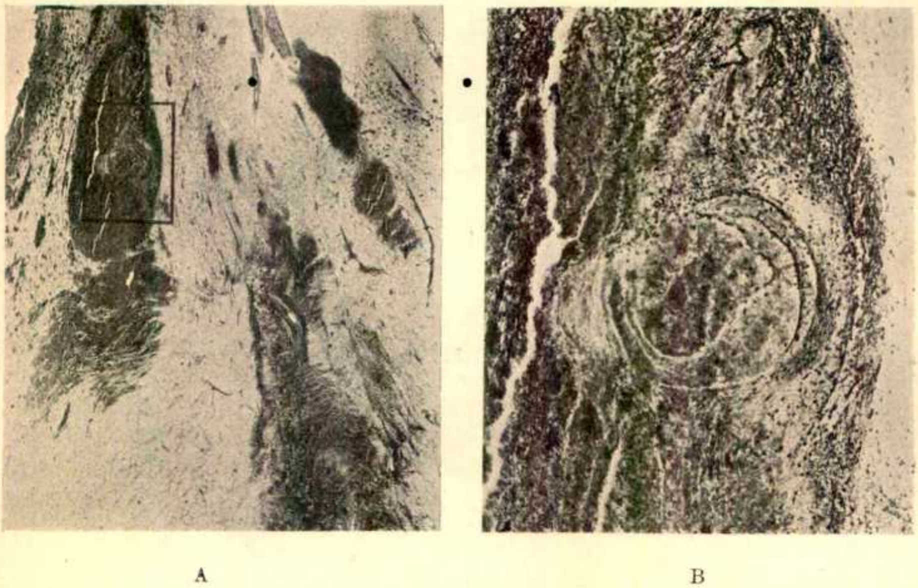
A B

FIG. 11.—*Case* 12. A. Low power magnification showing the multiplicity of hæmorrhages and their arrangement around necrotic vessels. In the marginal zones the extravasated blood follows the network of the fibre-tracts. (Cresyl violet.) B. Complete splitting up and necrosis of the layers of the walls of a vessel within a hæmorrhage. Fig. 6B shows the same process in an early stage. (Cresyl violet—high power.)

Post-mortem examination.—The dura was tense and there was a slight cerebellar pressure cone. There was a definite herniation of the left uncus through the incisura tentorii. There was a tumour, hæmorrhagic on its under surface in the left frontal pole. In the mid-brain there were multiple hæmorrhages from the central and peripheral vessels. The central hæmorrhages extended up to the level of the oculomotor nuclei. The hæmorrhages all appeared to be of the same age. The basal vessels appeared normal. The heart, aorta and kidneys showed no pathological changes.

Histological examination.—The tumour is a polar spongioblastoma.

A section of the brain-stem at the caudal level of the red nucleus shows multiple hæmorrhages in the area of the central ascending arteries. In each hæmorrhagic area a vessel, apparently the source of the hæmorrhage, is to be seen (fig. 11A). The vessel wall shows necrosis and the layers are partially split (fig. 11B). There is no glial reaction in the surrounding tissue. The ganglion cells in the involved areas have either entirely disappeared or show severe cell change. The extracerebral vessels in relation to the hæmorrhagic area are normal.

Hæmorrhages in the Mid-brain and Pons.

Case 13.—E. T. (Case No. 59/35), male, aged 47 (Dr. C. P. Symonds), was admitted to hospital on July 8, 1935. His symptoms began four months before admission, with focal convulsive seizures involving the right hand and face, weakness of the right arm and leg, and difficulty in speaking. These were followed within a month by loss of memory, drowsiness, loss of vision and increasing weakness of the right arm and leg.

Examination.—The patient showed speech disturbance and defect of memory. The optic discs were normal. There was a right hemiplegia. On the right side, sense of position, two-point discrimination, and vibration sense were greatly impaired.

Lumbar puncture performed July 9, 1935, showed a clear cerebrospinal fluid under 190 mm. water pressure, containing no cells, and a total protein of 0·075 per cent.

He had several convulsive seizures in hospital, and by July 18 had become quite drowsy. The edges of the optic discs were blurred and the right arm and leg had become spastic and powerless. He died on July 23, 1935.

Post-mortem examination.—The left parietal lobe bulged considerably and the convolutions in the upper part of the lobe were much widened and flattened. A cystic tumour, the size of a hen's egg, occupied the upper part of the parietal lobe. Very small nodules of tumour tissue were also found under the cortex of the right temporal lobe, near the vertex of the left frontal lobe, on the side of the mid-brain, and in the white matter of the cerebellum.

In the rostral part of the pons and the caudal part of the mid-brain there were multiple hæmorrhages, partly confluent, partly isolated, which seemed to be of the same age. The confluent hæmorrhages were from the central arteries. There was a small tumour nodule, the size of a pea, in the upper level of the ponto-cerebellar fibres and lying 2 mm. from the central hæmorrhage in the pons. The basal vessels showed no macroscopical abnormality.

Histological examination.—The tumour is a typical bronchial carcinoma of the oat-cell type.

The mid-brain hæmorrhages contain in their centre dilated vessels with amorphous walls. There is no tissue reaction round the hæmorrhage. The extracerebral vessels appear intact.

Hæmorrhages in the Mid-brain and Pons.

Case 14.—T. K. (Case No. 40/34), male, aged 49 (Dr. James Collier), was admitted to hospital on March 13, 1934. He gave a history of difficulty in reading for eighteen months preceding his admission. Weakness of the left arm and leg, and trouble with micturition began about two months before coming into hospital. He complained of headache when using his eyes for reading small print.

Examination.—The patient was drowsy and incontinent of fæces and urine. There was a left homonymous hemianopia. The optic discs were blurred and the retinal veins engorged. The pupils were irregular and inactive to light. There was bilateral ptosis of the lids, a marked left lower facial weakness, and a left spastic hemiparesis. All forms of sensation were impaired on the left side. Blood-pressure, systolic 105, diastolic 85. The patient died on March 19, 1934.

Post-mortem examination.—The dura was generally tense. The cerebral convolutions were flattened. There was a slight cerebellar pressure cone and the right uncus had herniated somewhat. There was an area of fluctuating swelling behind the Rolandic fissure and above the fissure of Sylvius on the right side. On incising here thin pus escaped. The cavity, about the size of a hen's egg, was thin walled.

In the upper third of the *pons* and at the level of the *posterior colliculi* there were small multiple hæmorrhages. Where the section was in the longitudinal direction of the vessels it could be seen that the hæmorrhage accompanied the vessel for some distance. The peripheral vessels were less affected than the central ones. The basal vessels appeared normal macroscopically.

There was a tumour in the region of the hilus of the lung.

Histological examination.—The tumour at the root of the lung is an oat-cell type of carcinoma.

The hæmorrhages in the pons contain necrotic ganglion cells with formalin pigment impregnation and dilated necrotic vessels which are situated in the centre of the hæmorrhagic area and are obviously the source of the hæmorrhage. There is no tissue reaction around the hæmorrhage. The right hippocampus and visual cortex are microscopically intact. The extracerebral vessels are normal.

DISCUSSION.

Before discussing the merely pathological aspect and the pathogenesis of the lesions described, it would be well to consider first their clinical significance.

The calcarine softenings and the lesions in the brain-stem, whether softenings or hæmorrhages, are morphologically in no way distinguishable from those seen in cases of cerebral vascular disease. It is quite probable, therefore, that the clinical picture of these lesions is similar to that encountered in apoplectic seizures. There is, however, this important difference; in a case of brain tumour where a vascular lesion intervenes the latter affects a patient who usually has already shown neurological symptoms which may have come on suddenly with unconsciousness due to the growth of the tumour itself. If every apoplectiform manifestation in cases of brain tumour indicated that a vascular lesion had occurred locally and independent of the neoplasm itself, it might be expected that such pathological findings would be encountered more frequently than, in fact, they occur. On the other hand, in cases where the patient is bedridden, drowsy and shows poor co-operation, sudden events in the clinical course of the illness may escape detection.

In examining our case histories from this point of view, we find some in which the clinical equivalent to the vascular lesions described appears rather clearly.

In Case 3, the patient had suffered from severe headaches after a lumbar puncture, but in the succeeding three days he appeared quite well. Then one morning he could not be roused and the degree of coma made an emergency ventricular tap necessary. He died the same day. The gross and microscopic appearance of the involved tissues is typical of a fresh ischæmic infarction of the cortex and a fresh hæmorrhage into the brain-stem. They represent the anatomical equivalent of the sudden final event in the patient's history.

In Case 4, coma set in one day before death. Here fresh hæmorrhages without any signs of connective tissue or glial reaction were found in the mid-brain and occipital lobe, and it is very likely that the final comatose state was connected with these hæmorrhages. Cases 8, 11 and 12 are very similar, and they all showed a final comatose or stuporous stage. In view of the fact that in these cases the brain-stem hæmorrhage was fresh, we are inclined to regard it as the final cause of death and the anatomical equivalent of the final clinical picture.

It is quite evident that a localized cortical softening, not accompanied by a vascular lesion in the lower brain-stem, does not necessarily produce an alarming clinical picture. Thus in Case 5 the patient noticed a visual disturbance some weeks before admission, and on examination showed a right homonymous hemianopia. Corresponding to the clinical picture there was an ischæmic infarction of the left visual cortex which from the histological appearance—shrinkage of the cortex and numerous gitter cell formation with marked fat inclusion—may have been several weeks old. Although not indicated by the clinical history, it is very probable that the visual disturbance came on suddenly as the result of the infarction of the visual cortex.

None of the cases showed focal symptoms which were suggestive of a pontine or mesencephalic lesion. In those cases in which the clinical picture gave any evidence at all of a lower brain-stem hæmorrhage the state of coma did not clear up sufficiently to permit an evaluation of pontine symptoms. This is all the more remarkable in that Bannwarth reports cases of cerebral tumours, complicated by brain-stem hæmorrhage, in which the diagnosis of a pontocerebellar angle tumour was made on the basis of the symptomatology.

From our experience we feel that when there is a sudden onset of profound unconsciousness, similar to certain apoplectiform pictures in other diseases, in a case of brain tumour it is suggestive of a complicating hæmorrhage in the lower brain-stem, even though this clinical picture also occurs in tumours without the complicating pontine hæmorrhage. Ponto-mesencephalic hæmorrhages always seem to be a fatal complication.

As regards the occipital lesions, the history in Case 5 shows that in cases of neoplasm in which a visual disturbance of cortical origin does not fit in with the remaining tumour symptomatology one must think of an occipital infarction which has no immediate local connection with the tumour itself.

The clinical history fails to give much information regarding the pathogenesis of the lesions under discussion. Surgical procedures *per se* can be excluded as a factor in their production. In ten of the fourteen cases reported no operative procedure had been carried out. Only in one case was there a time relation (Case 7) ; one day before death a craniotomy was performed and fresh pontine hæmorrhages were found on post-mortem examination. This may have been purely coincidental in this single case as such an association of events did not occur in the other cases. Therefore, we can state in accordance with Bannwarth and Rosenhagen that the vascular lesions described are not directly produced by cranial operations.

General vascular disease as a predisposing factor can be excluded. In Case 6, a single blood-pressure reading of 170 systolic, 120 diastolic was recorded. In another case (Case 10, female, aged 60) microscopical examination of the dissected basilar artery revealed an intimal proliferation of the type found in early arteriosclerosis. The smaller local vessels showed no significant change. These two cases alone constitute those in which vascular pathology, of no great consequence, however, was found. It is safe to say, from what is known of the pathological work which has been done on the problem of apoplexy in arteriosclerosis, that a plaque in the basal main stem of the artery, such as appeared in Case 10, was not responsible for the type of hæmorrhage which occurred. All the remaining cases showed normal extracerebral arteries, and the intracerebral vessels exclusive of those situated immediately within the hæmorrhagic areas also were normal.

From the previous reports in the literature by Rosenhagen and Bannwarth it may be gathered that the increased intracranial pressure and cerebral œdema seem to play an important role in the production of the pontine lesions. Although the authors differ in their explanation of the pathogenesis of the pontine hæmorrhages they concur in emphasizing the above factor. The majority of our cases, in which cerebrospinal fluid pressures (ventricular and lumbar) were recorded, show evidence of increased intracranial pressure. One case (Case 12) showed an extremely low lumbar cerebrospinal fluid pressure, but in view of the cerebellar pressure cone found in this case no conclusion can be drawn concerning the state of the intracranial pressure.

Not only do the clinical reports suggest evidence of brain swelling and increased intracranial pressure, but the anatomical findings reveal these as well. Such signs as herniation of parts of the temporal lobe through the incisura tento[illegible] cerebellar pressure cone, and bone erosion were observed in eight of [illegible]orted cases.

Without considering at [illegible]me whether the described vascular lesions are produced by mech[illegible]al obstruction or by functional abnormalities of the vessels such as spasm or vasoparalysis, it may be said that the increased intracranial pressure acting as the sole factor cannot be the cause of the lesions. Were this so they would occur oftener than is the case. There must be something in addition which finally acts on the vessels to produce the changes seen.

A consideration of certain topographical conditions is necessary before elaborating further on this problem. The posterior cerebral arteries shortly after coming off from the basilar artery arch backward and upward between the crus cerebri and the uncinate convolution. During part of their course they may come in close to the free edge of the tentorium. An intracranial process which produces a herniation of the uncus through the incisura, would be likely to compress the posterior cerebral artery so that the blood supply to the occipital lobe would be shut off. Thus a space-taking lesion above the tentorium might be sufficient to cause an obstruction of the posterior cerebral artery in this way. As has been shown by many observers, particularly those of the French school, Foix and Lévy (1927), Claude and Cuel (1927), and Ley (1931), a slowly developing obstruction to the arterial blood-flow may be compensated for, to an astonishing degree, by the anastomotic supply. This may be the reason for the infrequency of ischæmic lesions in the area supplied by the posterior cerebral artery. A slowly developing compression of the trunk of the artery would undoubtedly produce an organic change in the vessel wall and consequent thrombosis. Both from the fact that the occipital lesion is comparatively rare and that no organic changes of the vessel wall were found, we may conclude that the occipital lobe lesions were not the result of a gradual increase in intracranial pressure. We assume than an acute change in intracranial pressure relations, due either to an acute brain swelling or a sudden release of pressure in the subtentorial space, produces the train of events which lead to occipital lobe infarction. Even so, there is a question whether the merely mechanical occlusion of the artery by pressure from without is the actual cause of the infarction or whether repeated external mechanical irritation of the arterial wall produces a vasomotor disturbance. We cannot attempt an explanation of this question from our purely morphological investigation.

There is an essential morphological difference between the occipital and pontine lesions which have been described here. The occipital lobe lesion is a necrosis, confined to the grey matter only and may or may not be accompanied by capillary hæmorrhages. This is the typical ischæmic or hæmorrhagic infarction found in embolic or arteriosclerotic thrombotic lesions of the brain, i.e. it is typical of lesions produced by physical obstructions of arteries. These lesions, however, may also occur in arterial hypertension as shown by Neubürger (1930) and Hiller (1935).

The lesions in the brain-stem consist of multiple gross hæmorrhages. Their distribution is along the course of the arteries, arterioles or capillaries without any special predilection for the white or grey matter or anatomical structures, in contradistinction to the selective involvement of the cortical grey matter in the infarctions. This type of pontine lesion, as is known, is characteristic of the common apoplectic pontine hæmorrhage seen in arterial hypertension. To draw the analogy still closer, it was seen that the hæmorrhages tend to be related to the long ascending central branches of the basilar artery, which also is typical of apoplectic lesions due to other causes (Foix and Hillemand (1925), Schwartz (1930), Stern (1933); furthermore, the histological appearance of the pontine lesions is identical with that seen in ordinary apoplexy. All the changes found in apoplexies of arterial hypertension, which were first described by Rosenblath (1918) and confirmed since then by Lindemann (1924), Westphal and Bär (1926), and Schwartz (1930), were found in our cases (figs. 6B, 9D, 11A and B), viz. the delamination of parts of the vessel wall, the marginal accumulation of leukocytes, the partial dissection of the layers of the vessel wall, and the acute "arterio-necrosis," all changes which occur suddenly and simultaneously in different arteries not related to each other. The striking similarity of the lesions described here with the pontine hæmorrhages found in hypertension permits of two deductions. First, that Rosenblath's hypothesis, of toxic (renal) genesis of the arterial and tissue necrosis (the latter being an assumption only) which precedes the hypertensive cerebral hæmorrhage is untenable. Secondly, it may be assumed from the morphological identity of the lesions that their pathogenesis has some common denominator.

From an analysis of our cases it seems probable that the arterio-necrosis is a secondary phenomenon, the result rather than the cause of the hæmorrhage, a point which already has been emphasized, in hypertensive and traumatic cerebral hæmorrhages, by Staemmler (1927). Where the hæmorrhage is not massive the vessel wall elements are clearly distinguishable, the layers being partially delaminated, the cell interstices extremely widened by a relaxation of all the coats of the wall (fig. 6B), bringing about a diapedesis or even rhexis. Only the vessels within the areas of massive hæmorrhage are necrotic, which observation lends support to the view that arterio-necrosis is produced secondarily by the hæmorrhage.

What does the similarity of the histopathological appearance of the lesions we have described with the hæmorrhages in arterial hypertension indicate? Concerning the latter much remains in the realm of pure conjecture as regards pathogenesis. It has been established that in hypertension the muscularis of the arteries is under abnormally high tension. If the similarities are carried over to our cases it would mean that the arteries of the pons and mid-brain likewise were under a high tension, or, at any rate, that the mechanism which finally leads to the hæmorrhage is essentially the same in both arterial hypertension and cerebral tumours.

Animal experiments have shown that a sudden rise in the intracranial pressure which retards the blood circulation within the cranial cavity by compression of the vessels is regularly followed by an increase of the systemic blood-pressure (Wolff and Forbes (1928); Wolff and Blumgart (1929)). The systemic blood-pressure rises until the abnormal resistance in the intracranial vessels is overcome. This reaction can only be obtained by a sudden increase of the intracranial pressure, not by a slow gradual increase. Otherwise we should expect to find a constant arterial hypertension in most cases of cerebral tumour.

As the histological picture of the arteries in our case is identical with the acute changes found in association with the hæmorrhages in arterial hypertension, we abandon Bannwarth's view of an arterial hæmorrhage by mere congestion. It is much more likely that the same mechanism—rise of the systemic blood-pressure following a sudden rise of the intracranial pressure—applies here. Such a transient rise of the systemic blood-pressure may easily escape clinical observation.

If this be so, why are the hæmorrhages confined to the pontine branches of the basilar artery? There are several factors which produce a *locus minoris resistentiæ* in these arteries. We are in accord with Bannwarth's view that the effect of the intracranial pressure must be more marked near the outlet of the cranial cavity, i.e. foramen magnum.

Kolisko emphasized that the basilar artery lying fixed for a long distance parallel to a bony surface is more exposed to the increased intracranial pressure than the other basal arteries. This view, put forward to explain post-traumatic hæmorrhages, was adopted by Rosenhagen to explain the pontine hæmorrhages in brain tumours.

It is true that after the compression of an artery which produces ischæmia, the release of pressure may produce hæmorrhages in the terminal branches of this artery, as is known from the arteries of the extremities. Such hæmorrhages are petechial; one could so explain the petechial hæmorrhages in the neighbourhood of the iter and the 4th ventricle following trauma (Duret's hæmorrhages). The pontine hæmorrhages as we have seen them, however, are arterial, and, moreover, the complete absence of infratentorial tumours in our material and in that of Rosenhagen and Bannwarth indicates that the effect of compression of the basilar artery is insignificant.

It is generally known from the uncinate herniations and the notching of the peduncle that the increase of supratentorial pressure exerts its main effect on the rostral end and bifurcation of the basilar artery.

We explained thus the compression of the posterior cerebral artery. The softening in Case 6 (fig. 5) which was localized in the peduncle on the side opposite to the side of the tumour is presumably caused by the immediate compression of an arteriole. The same mechanism, however, may cause an arterial congestion of the basilar artery and make this area predisposed to the final hæmorrhage.

Thus, besides reflex rise of the systemic blood-pressure we have to consider a local predisposing factor, i.e. the congestion of the basilar artery by the partial obstruction in the area of its outflow. It still remains undecided why in one case the posterior cerebral artery and in another the basilar artery is more affected. It is probable that minute individual differences in the topography of this area account for the different behaviour.

SUMMARY AND CONCLUSIONS.

Vascular lesions in the brain-stem and calcarine cortex occurring in cases of space-taking lesion of the brain and in no immediate juxtaposition to the tumour itself have been studied in eighteen cases.

Fourteen cases are described clinically and pathologically. In five there was involvement of one or both occipital lobes, combined or not with lesions of the brain-stem. In the remaining cases only brain-stem lesions were found.

With the exception of one case (softening in the peduncular region), the brain-stem lesions consist of multiple fresh hæmorrhages from arteries. Histologically they resemble hæmorrhages in arterial hypertension. The occipital lesions are hæmorrhagic or ischæmic infarctions.

It is suggested that sudden changes in the pressure relationship between the supra- and infratentorial spaces lead to disturbance of the circulation in the area of the rostral end of the basilar artery. Compression of the posterior cerebral artery causes occipital infarction. Arterial congestion in the basilar artery causes a predisposition to hæmorrhages which are finally brought on by reflex rise of the systemic blood-pressure.

Surgical procedures seem to have no pathogenetic significance.

The clinical picture of the brain-stem hæmorrhages is that of a sudden onset of unconsciousness. They seem to be fatal in every case.

The occipital lesions have their clinical counterpart in apoplectiform manifestations or visual disturbances which complicate the neurological picture.

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OBSERVATIONS ON THE PATHWAYS TRANSMITTING THE SENSATION OF TASTE.

BY HENRY G. SCHWARTZ (ST. LOUIS) AND GRAHAM WEDDELL[1]
(LONDON).

From the Neurosurgical Service of Barnes Hospital and the Washington University School of Medicine, St. Louis, Mo.

INTRODUCTION.

LUSSANA (1869, 1871-72), on the basis of clinical and experimental observations, described a pathway for the transmission of gustatory sensation from the anterior two-thirds of the tongue. According to his description (fig. 1), which is now generally accepted, the impulses are carried by the chorda tympani, which joins the facial nerve *en route* to the geniculate ganglion; from this point fibres reach the brain-stem through the sensory portion of the 7th nerve (pars intermedia, or nervus intermedius of Wrisberg).

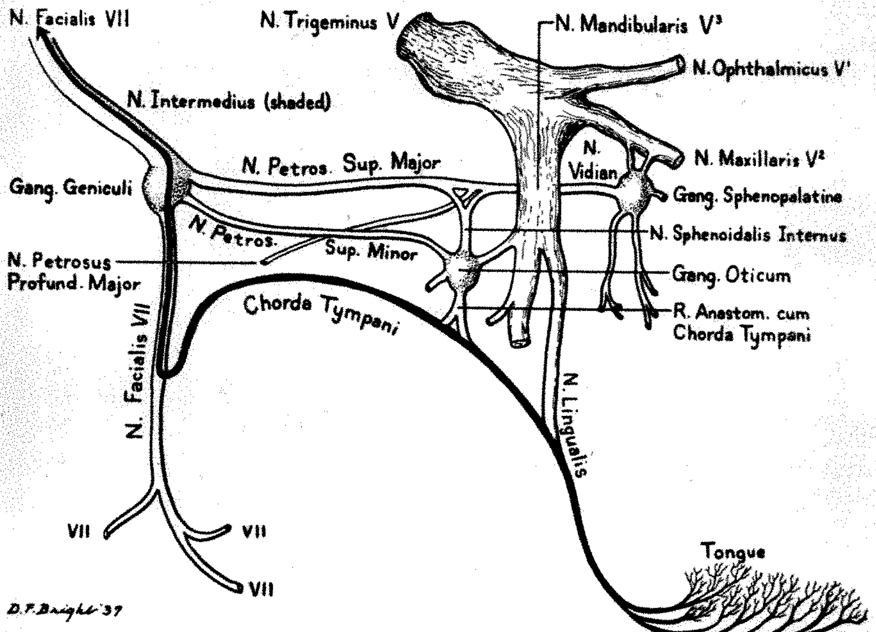

FIG. 1.—Diagram of Lussana's pathway for the transmission of gustatory impulses from the anterior two-thirds of the tongue.

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[1] Fellow of the Commonwealth Fund.

It is not the purpose of this report to present a review of the literature on the subject. This has been exceedingly well done by Cushing (1903) and Lewis and Dandy (1930). Cushing presented evidence in favour of Lussana's path, and Lewis and Dandy in a series of classical experiments upon humans came to the same conclusion. Subsequently Reichert and Poth (1933) and Reichert (1934) added confirmatory evidence.

Although the foregoing observations appear to be conclusive, no attempt has been made to reconcile the conflicting opinions scattered through the literature. Gowers (1880-82, 1893, 1902) and Schiff (1870, 1887, 1896) insisted that taste was mediated through the 5th nerve; Oppenheim (1911) and Harris (1920) concluded that the pathway may vary in different individuals. Recently, Carmichael and Woollard (1933), in a critical study of the 5th and 7th cranial nerves stated: "Though the evidence in favour of the 7th nerve carrying taste fibres, evidence which is derived from comparative anatomy, experimental inquiry and clinical observation, seems decisive enough, the loss of taste in so many of these 5th nerve cases is very puzzling, and we feel that no satisfactory explanation has yet been obtained."

The cases which form the basis of the present communication seem to explain some of the contradictory reports. We believe that the sensation of taste from the anterior two-thirds of the tongue reaches the brain by way of the geniculate ganglion and the nervus intermedius. Although the classical pathway of Lussana is applicable in the majority of instances, our series of observations suggests that there is some variability in the course of the gustatory fibres from the periphery to the geniculate ganglion. In certain individuals the impulses are transmitted during part of their course by way of the greater superficial petrosal nerve to the geniculate ganglion. From this point they are carried centrally in the classical manner.

MATERIAL AND METHODS.

Observations on sixteen patients are recorded. Of these, eleven had had trigeminal sensory root section by the temporal approach for relief of tic douloureux. In five patients radical mastoidectomy was performed. The cases were chosen from a group at Barnes Hospital within a three-month period. Except where otherwise noted, all special examinations were made by us and demonstrated to the neurosurgical staff.

The necessity of controlling the means of testing taste has been emphasized (Lewis and Dandy, 1930). Care must be taken to exclude diffusion of substances, olfactory influences, and guessing on the part of the patient. Three standard crystalline substances—cane sugar, sodium chloride and quinine sulphate—were used. The subject's tongue was protruded and the tip was held lightly with gauze by the examiner. Crystals of the test substance were moistened with tap water and applied to specific areas of the tongue. The use of moist crystals assured maximum concentration, and spread was more easily controlled. Because of difficulty in accurately controlling diffusion of acid or "sour" solutions, these categories of taste were omitted. After the test substance was applied to the protruded tongue, the patient was asked to point to the name of the taste experienced, a printed list of various tastes being held before the patient. Time of response was measured; no result was considered negative until sixty seconds had elapsed following application of the moist crystals. Between applications of substances, the mouth was rinsed with tepid water until the sensation of taste was no longer present. In all cases repeated examinations were made, and the sequence of substances tested was varied so that guessing on the part of the patient was satisfactorily excluded. As others have done, we found some variability of response in different individuals. Considerable patience may be required to obtain honest and intelligent responses, owing in large measure to patients' lack of familiarity with the test. Using the technique described in thirty cases of all types, including the sixteen presented here, no instances of so-called "taste blindness" were found.

OBSERVATIONS.

The material has been divided into several groups :—

Group I.—Differential section of the sensory root of the trigeminal nerve uncomplicated, i.e. without involvement of petrosal or facial nerves, and without taste loss.

Four such cases are reported here :—

Case 1.—I. M. B. (No. 57768), a 59-year-old white man, admitted on October 24, 1936, with a history of tic douloureux involving the right second division. Pre-operative neurological examination was negative. Special examinations of 5th and 7th nerves revealed no abnormality. No subjective taste disturbance. Tests of gustatory function produced normal, prompt responses for sweet, salt and bitter over both sides of tongue, front and back. On October 27, 1936, Dr. Ernest Sachs performed a differential section of the sensory root on the right side. The dura was easily stripped up from the temporal fossa, and the sensory root was exposed without difficulty. The petrosal nerves were not seen.

Post-operative course was uneventful. There was no facial paralysis. There was anæsthesia over all three divisions of the right trigeminal nerve, involving all forms of sensation, except recognition of large deformities of the skin. Deep pressure pain was increased from 0·25 kg. (pre-operative) to 2·0 kg. over all three divisions. No subjective taste disturbance. Taste was tested on October 30, 1936, with the following results.

	Right	Left
	Anterior 2/3	
Sweet[1]	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

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[1] In this and subsequent records of taste performance, "prompt" indicates the response given two to three seconds after application of the test substance.

Case 2.—M. E. T. (No. 58352), a 54-year-old white woman, admitted on November 29, 1936, with a history of tic douloureux involving the second division on the left side. The patient had hypertension with arteriosclerotic heart disease. Neurological examination revealed no abnormalities except for slightly less acute corneal reflex on the left than on the right. Otherwise the 5th nerve was normal. No facial weakness. No subjective or objective taste disturbance.

On November 30, 1936, Dr. Sachs performed a differential section of the left sensory root. The petrosal nerves were not seen.

Post-operative course was uneventful. There was anæsthesia over the third division, including the left half of the tongue. There was hyperæsthesia over the second division. The first division was essentially spared. Corneal reflex on the left was slightly less active than on the right, as before operation. No facial weakness. No subjective taste disturbance. Taste was tested on December 8, 1936:—

	Right	Left
	Anterior 2/3	
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

The patient returned for a visit on December 28, 1936, and again on April 2, 1937. She was completely free of pain. Sensory loss as noted above; no taste disturbance.

Case 3.—N. E. F. (No. 59148), a 53-year-old white woman, admitted on January 18, 1937, with a history of tic douloureux of twelve years' duration.

Originally confined to the third division, pain subsequently spread to the first and second divisions, on the right side. There was a definite trigger zone inside the right lower lip. The only abnormality revealed on examination consisted of slight weakness of the right pterygoids. This was considered to be due to multiple peripheral alcohol injections which had been made earlier without relief. No sensory changes over domain of trigeminal nerve. Facial nerve intact. No subjective taste disturbance. Pre-operative tests revealed the following :—

	Anterior 2/3	
	Right	Left
Sweet	20 sec.	10 sec.
Salt	15 sec.	Prompt
Bitter	10 sec.	10 sec.

The posterior part of the tongue could not be tested due to the patient's inability to open her mouth sufficiently widely.

Differential sensory root section on the right on January 19, 1937. The procedure was uncomplicated. Dr. Sachs noted that the middle meningeal artery was absent. Petrosal nerves were not exposed in the field, nor was the sulcus n. petrosi superficialis majoris of the temporal bone seen.

The post-operative course was uneventful. No facial weakness. There was complete anæsthesia over the third division, including the right half of the tongue and hyperæsthesia over the first and second divisions. Deep pressure pain was increased from 0·5 kilograms (preoperative) to 1·0 to 2·0 kg. after operation. No subjective taste disturbance. Taste was tested on January 23, 1937, with the following results :—

	Anterior 2/3	
	Right	Left
Sweet	7 sec.	7 sec.
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

Case 4.—B. L. H. (No. 59180), a 35-year-old white woman, admitted on January 19, 1937, with history of tic douloureux involving the second division on the left side. Neurological examination, including special examinations of 5th and 7th nerves, was negative. No subjective taste disturbance. This patient was not tested by us before operation, but the routine neurological examination is recorded as showing " taste normal and equal on both sides."

On January 20, 1937, differential section of left sensory root was performed by Dr. Sachs. The dura in this case was very friable and was opened without complete stripping from the floor of the temporal fossa. The petrosal nerves were not exposed or damaged.

Post-operative course was uneventful. No facial weakness. There was anæsthesia of the third and hypæsthesia of the second divisions. Sensation was intact over the first division. The right side of the tongue was anæsthetic. No subjective taste disturbance. Taste was tested on January 24, 1937, with the following results :—

	Anterior 2/3	
	Right	Left
Sweet	10 sec.	7 sec.
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
	Posterior 1/3	
Sweet	5 secs.	Prompt
Salt	5 secs.	Prompt
Bitter	Prompt	Prompt

Comment.—The observations on the patients in this group confirm the fact that taste is not transmitted by the second or third divisions of the trigeminal nerve. It has been proved conclusively (Lewis and Dandy, 1930) that gustatory impulses are not carried by any portion of the sensory root. These cases are included in the present study to demonstrate that there was no interference with the petrosal nerves nor any apparent injury to the geniculate ganglion.

Group II.—Differential Section of Sensory Root followed by Disturbance of Taste on the Homolateral Side.

This group embraces several categories.

A.—Sensory Root Section with Facial Paralysis and Taste Loss.

No attempt will be made to give the individual records of at least four available instances in which facial paralysis appeared after operation for trigeminal section, accompanied by loss of taste over the homolateral anterior two-thirds of the tongue. These cases were operated upon before we became aware of the importance of the greater superficial petrosal nerve. Accordingly there is insufficient data upon which to form any unorthodox opinion. The only thing that can be said is that the operative procedures in these four cases were complicated by technical difficulties. In view of the occurrence of facial paralysis in these four cases, it is conceivable that the hemigeusia may have resulted from injury to the geniculate ganglion by force transmitted through the petrosal nerves. Such a mechanism was postulated by Dixon (1897) and Lewis and Dandy (1930).

Besides the category just alluded to, however, we have found several patients, with post-operative gustatory loss, observations on whom are significant.

B.—Differential Section with Injury to Greater Superficial Petrosal Nerve, Facial Paralysis and Taste Loss.

Case 1.—C. A. W. (No. 57621), a 57-year-old white woman, admitted on October 15, 1936, with a history of tic douloureux involving the second and third divisions on the right side. There was a trigger zone inside the right lower lip. Neurological examination, including special examination of the 5th and 7th nerves revealed no abnormality. No subjective taste disturbance. Pre-operative taste examination showed prompt responses for all substances on both sides.

On October 17, 1936, Dr. Sachs performed a differential section of the right sensory root. During the operation it was necessary to cut several bands in the region of the petrosal nerves, because of dural adhesions. This was done deliberately with the hope of preventing facial paresis due to traction.

Post-operatively there was almost complete lower facial paralysis on the right side. There was anæsthesia over the second and third divisions of the trigeminal nerve, with hypæsthesia of the first division. No subjective taste disturbance. Taste was tested on October 22, 1936 :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	Prompt
Salt	Absent	Prompt
Bitter	Absent	Prompt
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

The patient returned on December 21, 1936. Exactly the same findings were present; there was no evidence of return of facial nerve function. On March 17, 1937, there was some slight recovery of facial function; sense of taste was still absent on the right anterior two-thirds of the tongue.

Case 2.—M W. M. (No. 57860), a 76-year-old white woman, was admitted on October 29, 1936, with a history of tic douloureux of five years' duration. All three divisions on the left side were affected. There was a trigger zone inside the left nostril. General physical examination showed hypertensive heart disease. The only abnormal neurological finding consisted of absent corneal reflex on both sides, although both corneæ were sensitive. The facial nerve was intact. No subjective or objective taste disturbances.

On November 3, 1936, Dr. Sachs performed a differential section of the left sensory root. The operation was complicated by extremely friable dura and unusual bleeding from dural and periosteal vessels. There was a great deal of trauma to the superficial petrosal nerves.

Post-operatively there was anæsthesia over the second and third divisions, except for preservation of sensation of very light touch (cotton wisps) and normal deep pressure pain. There was slight facial weakness on the left side. Taste was tested on November 15, 1936 :—

	Anterior 2/3	
	Right	Left
Sweet	Prompt	Absent
Salt	Prompt	Absent
Bitter	Prompt	Absent
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

On December 13, 1936, the patient returned for re-examination. Facial paresis had improved markedly; only the slightest weakness of the left orbicularis oculi remained. Tests of gustatory function at this time showed exactly the same findings as those recorded above.

Comment.—In these two cases there was damage to the superficial petrosal nerves, and indirect injury to the facial. The resultant loss of taste on the homolateral anterior two-thirds of the tongue can, of course, be explained (as the cases in sub-group A) on the basis of a geniculate ganglion lesion, and it might be reasonably postulated that petrosal nerve trauma was not the primary factor involved. However, the possible importance of the petrosal nerves cannot be dismissed entirely, even though the mass of evidence is preponderantly against their playing a direct rôle.

C.—Sensory Root Section with Section of Greater Superficial Petrosal Nerve, without Peripheral Facial Paralysis, and with Taste Loss.

The patient, A. A. McN. (No. 59153), a 50-year-old white woman, was admitted on January 18, 1937, with a history of tic douloureux involving the second division on the right side of three years' duration. Neurological examination was negative. There was slight facial asymmetry due to partial adentia; there was a suggestion of slight central facial weakness on the right. Special examinations revealed no abnormality of the 5th nerve. No subjective taste disturbance. Pre-operative taste test revealed somewhat sluggish responses on both sides over the anterior two-thirds of the tongue. Sluggishness of response was thought to be possibly associated with foul breath; the patient had almost given up the use of a toothbrush because of pain.

	Anterior 2/3	
	Right	Left
Sweet	10 sec.	10 sec.
Salt	8 sec.	10 sec.
Bitter	5 sec.	5 sec.

The posterior one-third of the tongue could not be tested because of pain.

On January 19, 1937, Dr. Leonard T. Furlow performed differential section of the right sensory root. The dura was easily stripped back and intentionally dissected farther posteriorly than usual to expose the sulcus n. petrosi superficialis. The petrosal nerves were clearly visible in the depths of the sulcus. Without further dissection and without traction a segment of the greater superficial petrosal nerve was excised (microscopic sections subsequently showed this segment to consist of numerous large myelinated fibres). Following this procedure, dissection of the dura was resumed anteriorly and the operation was then carried out in the usual manner.

Post-operative course was uneventful. There was complete anæsthesia of the third division, including the right half of the tongue, and hypæsthesia of the first and second divisions. No facial weakness. No subjective taste disturbance. Taste was tested on January 24, 1937 :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	10 sec.
Salt	Absent	10 sec.
Bitter	Absent	Prompt

The patient returned for re-examination on February 21, 1937, and May 1, 1937. General condition excellent, patient entirely free of pain. Sensory loss as before. No facial weakness or subjective taste disturbance. Gustatory function :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	Prompt
Salt	Absent	Prompt
Bitter	Absent	Prompt

Comment.—This record we regard as especially significant. Th greater superficial petrosal nerve was deliberately cut, in a relatively easy operative procedure, without any trauma to the geniculate ganglion. Although prior to operation there was thought to be slight central facial weakness, there was no pre-operative taste loss. Following operation, central facial weakness was no longer evident ; there was no sign of peripheral facial weakness, but there was hemigeusia over the anterior two-thirds of the tongue. It may be concluded that in this case taste was transmitted, for part of its course, by the greater superfical petrosal nerve.

Group III.—Radical Mastoidectomy with Facial Paralysis and with Loss of Taste.

The chorda tympani, after entering the tympanum through the aperture of the canaliculus chordae, courses anteriorly on the upper part of the tympanic membrane in the notch formed by the crus of the incus medially, and the anterior process of the malleus laterally ; it then passes above the tensor tympani muscle to the petro-tympanic fissure. It is apparent, therefore, that the chorda tympani cannot escape if the tympanic ossicles are removed.

In the cases of this and the following group, radical mastoid operations, with complete removal of the ossicles, were performed by Drs. M. F. Arbuckle and A. C. Stutsman. We wish to express our gratitude to them for permission to use this material, which represents not a carefully selected group, but simply five patients who happened to be available in the hospital at about the same time.

Case 1.—P. D. W. (No. 58867), a 27-year-old white school teacher, was admitted on January 4, 1937, complaining of chronic discharge from the right ear for eighteen years. During exacerbations of the disease the patient noticed taste deficiency on the right side of her tongue.

On January 4, 1937, right radical mastoidectomy with removal of the ossicles was done. Post-operatively, neurological examination was negative. Special tests revealed no abnormality of the 5th or 7th cranial nerves. Taste was tested on January 8, 12 and 17, 1937:—

	Anterior 2/3 Right	Left
Sweet	Absent	Prompt
Salt	Absent	Prompt
Bitter	Absent	Prompt
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt..	Prompt	Prompt
Bitter	Prompt	Prompt

Case 2.—O. R. K. (No. 59196), a 24-year-old white man, was admitted on January 19, 1937, with a history of chronic discharge from the right ear of four years' duration. No subjective taste disturbance.

On January 20, 1937, right radical mastoidectomy, with removal of the ossicles and a portion of the tympanic membrane, was performed. Post-operatively, neurological examination was negative, including special tests of the 5th and 7th cranial nerves. Taste was tested on January 25, 1937:—

	Anterior 2/3 Right	Left
Sweet	Absent	30 sec.
Salt	Absent	20 sec.
Bitter	Absent	Prompt

Case 3.—W. R. S. (No. 56500), a 49-year-old white man, was admitted to the nose and throat service of Barnes Hospital on November 4, 1936. He had been admitted previously on August 17, 1936, complaining of chronic discharge from both ears. A simple mastoidectomy had been performed on August 18, 1936. This was followed by sinus thrombosis, requiring secondary incision with drainage of the lateral sinus and ligation of the left jugular vein. On the second admission, the patient showed signs of lung abscess, in addition to the persistent left aural discharge. On December 1, 1936, thoracostomy with drainage of a large empyema cavity was performed by Dr. Brian Blades. The patient recovered from this procedure to permit a left radical mastoidectomy on January 9, 1937. Post-operative course was smooth. Examination showed no abnormal neurological findings, except for taste.

Taste was tested on January 22, 1937, and again on February 7, 1937:—

	Anterior 2/3 Right	Left
Sweet	Prompt	Absent
Salt..	Prompt	Absent
Bitter	Prompt	Absent

Comment.—These cases represent pure lesions of the chorda tympani and demonstrate the dependence of the sensation of taste on this nerve.

Group IV.—Radical Mastoidectomy without Facial Paralysis and without Loss of Taste.

Case 1.—M. L. J. (No. 58919), a 57-year-old white woman, was admitted on January 5, 1937. There was a history of chronic discharge from the right ear following acute otitis media, seven years previously. She had never noticed any difficulty in tasting; indeed, her sense of taste, developed through years of preparing highly-seasoned German dishes, was known to be extraordinarily acute. Olfactory sense, however, was poor due to frequent obstruction of the nasal passages by mucous.

Right radical mastoidectomy on January 6, 1937. The facial canal was exposed. Auditory ossicles were found in the remaining fragment of the drum and were removed. Post-operatively there was no abnormality of the 5th or 7th nerves; no subjective taste disturbance. Taste was tested on January 9, 1937. The responses were phenomenally rapid, answers being given immediately on touching the tongue with the test material.

	Anterior 2/3	
	Right	Left
Sweet	Instantaneous	Instantaneous
Salt	Instantaneous	Instantaneous
Bitter	Instantaneous	Instantaneous
	Posterior 1/3	
Sweet	Instantaneous	Instantaneous
Salt	Instantaneous	Instantaneous
Bitter	Not tested	Not tested

The examination was repeated on January 11, 1937 :—

	Anterior 2/3	
	Right	Left
Sweet	Instantaneous	Instantaneous
Salt	Instantaneous	Instantaneous
Bitter	Instantaneous	Instantaneous

Case 2.—C. E. T. (No. 58484), a 24-year-old white woman, was admitted on December 6, 1936, with a history of discharge from the right ear of three months' duration. Nine years previously the patient had acute otitis media, which was treated by incision of the drum. Following that episode there were intermittent periods during which she was troubled with discharge from the affected ear. No subjective taste disturbance.

On December 7, 1936, right radical mastoidectomy was performed. The middle ear and antrum were filled with granulation tissue; the ossicles had been partially absorbed. The mass was removed, including a small persistent remnant of the drum anteriorly. Post-operatively, the 5th and 7th nerves were normal. There was no subjective taste disturbance.

On January 12, 1937, taste was tested :—

	Anterior 2/3	
	Right	Left
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Absent	Prompt
	Posterior 1/3	
Sweet	Absent	45 sec.
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

It should be noted that although salt was equally and promptly recognized on both sides of the anterior two-thirds of the tongue, the patient stated that the sensation was not quite as distinct on the right as on the left. Sweet was tasted equally distinctly on both sides. On January 30, 1937, the patient was re-examined. All substances were recognized promptly and equally, and there was no subjective difference :—

	Anterior 2/3	
	Right	Left
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

Comment.—In these two cases, the chorda tympani was cut near its point of union with the facial nerve. Schiff (1870) contended that, in animals, section of the chorda tympani at this point is not invariably followed by taste loss. However, since Blau's (1879) accurate observations on a patient with a fistula of the middle ear, there has been no suggestion that taste is not carried by the chorda tympani. In the recent literature, Reichert and Poth reported four cases in whom the chorda tympani had been cut in the course of radical mastoidectomy; each of these showed hemigeusia on the homolateral anterior two-thirds of the tongue.

We are aware, therefore, that the preservation of taste in two of our cases is a most unusual and unexpected finding. It should be emphasized that, although the incidence is two out of five patients included in this report, we believe that the percentage is probably much smaller, and that the appearance of these two cases has been merely fortuitous. It must be concluded, however, that, in at least these two cases, the impulses of taste are carried, for at least part of their course, by a pathway which does not involve the proximal segment of the chorda tympani.

SUMMARY OF CASES PRESENTED.

Group I.—Differential Section of the Sensory Root, uncomplicated.

Four cases are noted, in which sensory root section was done, without interference with the petrosal nerves or injury to the geniculate ganglion. Taste was preserved, thus showing that gustatory impulses are not transmitted by the second or third divisions of the trigeminal nerve.

Group II.—Differential Section followed by Homolateral Taste Disturbance.

A. Four instances in which facial paralysis appeared post-operatively, accompanied by taste loss over the anterior two-thirds of the tongue. Because of operative trauma, the results may be said to have depended upon possible injury to the geniculate ganglion by force transmitted through the petrosal nerves.

B. Two cases, with known injury to the petrosal nerves and indirect trauma to the facial nerve. In these there was hemigeusia.

C. One case, with deliberate excision of a portion of the greater superficial petrosal nerve, without trauma to the facial nerve, and with loss of taste over the homolateral anterior two-thirds of the tongue.

Group III.—Radical Mastoidectomy without Facial Paralysis and with Taste Loss.

Three cases in which the chorda tympani was excised during the course of radical mastoidectomy, followed by preservation of facial innervation, with loss of taste over the homolateral anterior two-thirds of the tongue.

Group IV.—Radical Mastoidectomy without Facial Paralysis and with Preservation of Taste.

There are two cases in this group, in which taste was preserved although the chorda tympani was excised during radical mastoidectomy.

DISCUSSION.

From the observations on the single patient in Group II *C*, it must be concluded that the greater superficial petrosal nerve may at times transmit the sensation of taste. The question immediately arises concerning the complete pathway involved. Schiff (1870, 1887, 1896) had suggested that taste impulses were carried to the geniculate ganglion by the chorda tympani; transmission then occurred from the ganglion by way of the greater superficial petrosal nerve to the sphenopalatine ganglion; thence by way of the second division of the 5th nerve to the gasserian ganglion, and finally through the sensory root to the central nucleus. On the basis of our own observations and the reports in the literature, we do not believe that the 5th nerve is in any way involved with the transmission of taste.

There is adequate anatomical and embryological (Dixon, 1897; Hunt, 1937; Larsell and Fenton, 1928; Yagita, 1914) evidence that the greater superficial petrosal nerve forms, with the chorda tympani, the most important portion of the sensory system of the 7th nerve, arising from cells of origin in the geniculate ganglion; the small superficial and both deep petrosal nerves are not a part of the geniculate system. This evidence in itself would serve to invalidate Schiff's theory. It is reasonable to assume that sensory impulses which reach the greater superficial petrosal nerve must be conveyed centralwards to the geniculate ganglion.

The exact mechanism by which gustatory impulses reach the greater superficial petrosal nerve remains unsolved. During the course of his experiments Schiff (1870) found that, in some cases, section of the lingual nerve above its point of union with the chorda tympani was followed by partial loss of taste; also, as noted previously, he observed that section of the proximal segment of the chorda tympani did not always result in taste loss. Accordingly he considered that not all the taste fibres passed through the chorda tympani, but that part passed through the lingual. In offering an alternative pathway, therefore, he postulated that taste may be carried through the lingual to the otic ganglion, by way of an inconstant branch. From this point, he stated the impulse might be carried to the geniculate ganglion by the small superficial petrosal nerve, and finally away from the ganglion by way of the great superficial petrosal. Morphological evidence, previously offered, does not permit ascribing such functions to the petrosal nerves. Although it is improbable, we must admit the possibility that impulses may pass from the lingual, by an inconstant branch, to the otic ganglion. This connection is so inconstant (Hyrtl, 1866), however, as to render such a course doubtful.

If the participation of the lingual nerve be dismissed, it would be justifiable to assume some connection from the chorda tympani which would serve as a shunt. The cases in Group IV demonstrate that, in some instances, section of the chorda tympani in the middle ear is not followed by hemigeusia. It follows, therefore, that a communication must be given off by the chorda tympani, distal to the tympanum and proximal to its point of union with the lingual nerve. According to Quain (1895), Poirier and Charpy (1901) and Rauber (1909) there is a communication which leaves the chorda tympani, just above its junction with the lingual, and joins the otic ganglion. From the otic ganglion, these same anatomists describe the internal sphenoidal nerve which connects with the vidian nerve. At the point where the large superficial and deep petrosal nerves unite to form the vidian, Quain and Rauber illustrate a bifurcation of the internal sphenoidal nerve, with one limb in intimate relation with the greater superficial petrosal nerve.

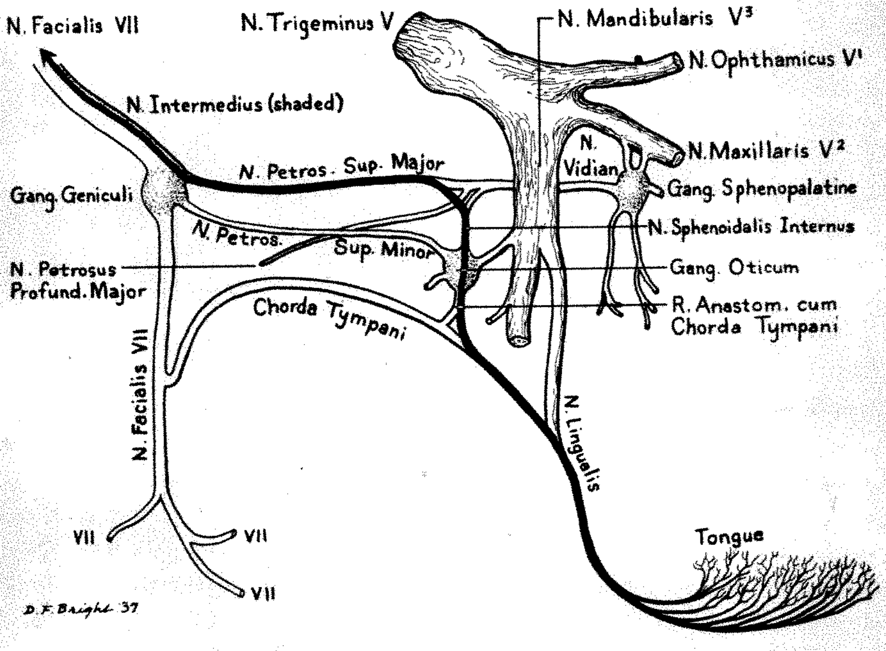

FIG. 2.—Suggested pathway for taste transmission from the anterior two-thirds of the tongue in a limited number of cases.

Until further evidence is obtained, a pathway for taste sensation, other than the usual course first advocated by Lussana, may be postulated as follows. The impulse is transmitted by the chorda tympani to the otic ganglion; from there, by way of the internal sphenoidal nerve, to the greater superficial petrosal nerve; thence to the geniculate ganglion and nervus intermedius, to the brain-stem (fig. 2). This is the probable course of taste fibres in a small percentage of cases; but we believe that in the majority of instances the classical pathway of Lussana is correct.

The implication of the greater superficial petrosal nerve in the mechanism of taste transmission may serve to explain some of the apparent discrepancies in the literature. It is not at all improbable that operative interference with, or alcohol injection of, the gasserian ganglion, involves secondary damage to the petrosal nerve. This may account for some of the cases of taste loss in trigeminal lesions reported, among others, by Gowers (1880-82, 1893), Harris (1926), Carmichael and Woollard (1933).

The importance of sparing the greater superficial petrosal nerve in operating in the temporal fossa is at once apparent; not only because of possible secondary trauma to the geniculate ganglion by traction, but also because of the possible effect of petrosal nerve injury alone. In the temporal approach for trigeminal root section, care should be taken to dissect the dura from the floor of the fossa as gently as possible. In addition dissection should be confined to the region anterior to the intracranial course of the petrosal nerve, until the dura propria over the ganglion is incised. In this way the petrosal nerve is kept entirely outside the operative field.

CONCLUSIONS.

(1) It is concluded that in certain individuals the greater superficial petrosal nerve forms part of the pathway for transmission of taste from the anterior two-thirds of the tongue. Gustatory impulses may pass from the chorda tympani by way of the otic ganglion and internal sphenoidal nerve to reach the greater superficial petrosal nerve; from this point they are carried by way of the geniculate ganglion and nervus intermedius into the pons.

This conclusion is based chiefly upon the following observations: (*a*) Loss of taste in one patient following excision of the greater superficial petrosal nerve; (*b*) preservation of taste in two cases following section of the chorda tympani.

(2) Additional cases are presented in which taste impulses follow the classical course, by way of the chorda tympani directly to the geniculate ganglion and nervus intermedius.

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A CASE OF PRIMARY GENERALIZED AMYLOID DISEASE WITH INVOLVEMENT OF THE NERVES.

BY S. DE NAVASQUEZ AND H. A. TREBLE,
The Department of Pathology, Guy's Hospital Medical School.

SO-CALLED primary generalized amyloid disease unassociated with antecedent infection is now well recognized, and several clinical and pathological types have been described. Of the clinical forms, the combination of unexplained cardiac failure, peripheral neuritis, and diarrhœa forms the salient feature in the majority of reported cases. In the present case this association of symptoms first suggested the tentative diagnosis of beri-beri.

We have been unable to find any reference in the accounts of published cases to amyloid disease involving the nerves. Where the signs and symptoms of peripheral neuritis have been present they have been attributed to the amyloid infiltration affecting the peripheral blood-vessels.

Two reasons have prompted us to publish our findings on this case. In the first place, the pathological examination of the nervous system shows that in generalized amyloid disease infiltration may occur in the peripheral nerves, as well as in the heart and elsewhere. Secondly, its similarity, both clinically and pathologically, to other cases of primary amyloid disease, and in particular to a case of hypertrophic polyneuritis described by De Bruyn and Stern (1929)[1], may serve to draw attention to this occasional involvement of the nervous tissue by amyloid infiltration as a possible explanation of the peripheral neuritis which may accompany this uncommon though well-defined disease.

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[1] Through the kindness and interest of Dr. J. G. Greenfield, one of us (S.DeN.) has been able to examine and compare the posterior root and sympathetic ganglia and peripheral nerves from De Bruyn and Stern's case, and there can be little doubt that the "plasmatic bodies" which they described are nodular deposits of amyloid. This is confirmed by the severe infiltration which is present in the arteries and perineurium. Unfortunately, it is impossible to employ special stains for amyloid, owing to the age of the material. The histological appearance of the ganglia and nerves in sections stained with hæmotoxylin and eosin and Van Gieson's method are so strikingly similar to our case that it leaves little room for doubt.

CASE REPORT.

Christopher A., aged 36, was admitted to Guy's Hospital complaining of diarrhœa, dizziness on exertion and gross muscular wasting and weakness.

His father had died at a great age, and his mother was alive and well. He had eleven siblings, one of whom was killed in the war; the rest were well. No other member of his family had ever suffered from symptoms resembling his own. He had married eleven years previously and had a daughter, aged 9, born at seven months. Another premature child died aged 2 months. There were no miscarriages and his wife was healthy. He denied any venereal infection.

He was apprenticed as an engineer in boyhood and had been in this occupation ever since. At no time had he worked with lead or in circumstances where any of his colleagues acquired any industrial disease.

Until four years before his admission he had had a healthy athletic life. At this time he had become an engineer's foreman, and no longer had time for his athletics. Up to this time he had never been ill or seen a physician. In the autumn of that year he had developed a series of minor carbuncles on his left forearm and face, none of which had been severe enough to leave more than a small pitted scar. These carbuncles had persisted for some weeks, and had been followed by an occasional septic spot ever since. None of these was present during his admission.

Two years previous to admission he had developed a nocturnal diarrhœa, passing about five loose motions in the night, but none by day. He began to feel physically weak and became impotent. About this time he developed bilateral hydroceles which slowly increased to a considerable size. Gradually he became weaker, his muscles wasted, and he became increasingly short of breath and dizzy on exertion. On one or two occasions after short brisk exertion he had become momentarily unconscious.

A year before admission he was seen at Guy's Hospital Out-patients, and was found to have a hæmoglobin of 58 per cent. He was treated for this anæmia with large doses of Blaud's pill without symptomatic improvement. His diarrhœa now occurred by day and night, and urgency of defæcation developed. The stools were very loose, but not otherwise abnormal. At this time he developed difficulty of micturition, passing a very small stream with much effort. He was compelled to give up his work on account of his weakness and shortness of breath.

His appetite remained good throughout the duration of his illness, and he continued his habit of eating a generous diet, including plenty of fresh fruit, meat and vegetables. His alcohol and tobacco consumption was very moderate.

During the course of his illness he developed numerous telangiectases about his face and neck, which bled on the slightest trauma, and at times he bruised with extreme ease.

On examination at time of admission he was 5 ft. 9 in. in height, and

8 stone 10 lb. in weight. There was gross wasting of the voluntary muscles, but his subcutaneous fat was normal. His skin generally, but especially where it had been exposed to light, was of an olive green colour, accentuated by contrast with the telangiectases and ecchymoses about his face and neck. This colour was not jaundice, his sclerotics being of normal hue. There were no local thickenings or cutaneous deposits. Neither fingers nor toes were clubbed.

Cardiovascular system : He had a regular pulse of 70 to 90. The blood-pressure was 135/100. A soft systolic murmur was heard over the whole præcordium, and gallop rhythm was present on all occasions. There was slight œdema in the lumbar region and over the tibiæ, but no abnormal filling of the veins of the neck was seen. Measured orthodiagraphically, the transverse diameter of his chest was 26 cm. and of his heart 15·3 cm. There was a uniform enlargement of all its chambers. Numerous X-rays taken during his eight weeks' stay in hospital revealed little change in its size and shape. An electrocardiogram taken soon after admission showed some inversion of T.2 and T.3 (fig.1). This inversion became slightly less on later occasions.

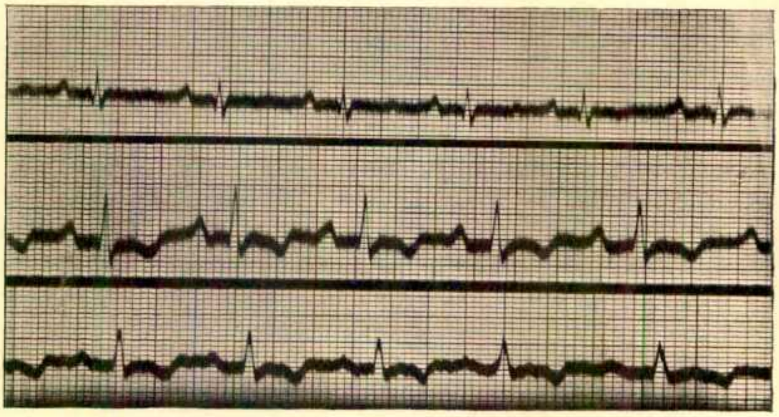

FIG. 1.—Electrocardiogram showing some inversion of T.2 and T.3.

Respiratory system : No abnormality was detected.

Alimentary system : His tongue was very smooth and clean, the edges showing almost complete atrophy of the filiform papillæ. It was pale, but neither swollen nor sore. His abdomen was normal. Nothing abnormal was detected on rectal examination. His liver, spleen and kidneys were not palpable.

Genito-urinary system : Bilateral hydroceles of considerable size were present. His testes and penis were unusually large, but otherwise normal.

His urine (sp. gr. 1010 to 1018) was neutral and constantly contained a good trace of albumin. Occasionally he passed some bright blood with the urine, either mixed with it, or at the end of micturition. No sugar was found on any occasion.

Central nervous system: His personality was cheerful, and he was at all times co-operative. His intelligence was above the average. The optic discs appeared normal.

His pupils were small, regular and central, but did not react to light and only sluggishly on convergence. There was no ptosis. He occasionally had some photophobia. His other cranial nerves showed no abnormality.

The muscles of both limbs and trunk were grossly wasted and proportionately weak, so that on admission he was unable to walk, and had difficulty in turning about in bed. His arm-jerks were present but very feeble, and his knee and ankle jerks were absent.

No abnormalities of the senses of touch, pin-prick, heat, cold, vibration, position or movement were demonstrated.

Muscular co-ordination was good so far as weakness allowed of its investigation. His muscles and tendons were not abnormally tender, though he complained of occasional cramp-like pains at night. The peripheral nerves were not unusually palpable, and the external popliteal and ulnar nerves especially felt of normal size.

Other organs: There was no enlargement of the lymph-glands nor signs of abnormality of the glands of internal secretion.

Laboratory findings: Test meal—achylia, some delay in emptying. Bile present in all specimens.

Fæces examination: Slightly alkaline, no excess of fats, no meat fibres or starch granules. Occult blood tests consistently negative, except on one occasion following epistaxis.

Alimentary X-ray: Stomach and duodenum, normal in all respects. In one hour, head of meal in jejunum; in three hours meal already reached cæcum and colon; in five hours a trace in the stomach, bulk in the cæum and rectum; appendix canalized and apparently normal, colon normal; in twenty-four hours, all evacuated.

Cerebrospinal fluid: Pressure 90 mm. no block, fell to 0 after 5 c.c. were removed. Fluid; clear, 6 red cells, and 1 lymphocyte per cmm. Protein, 160 mgm. per cent. (Mestrezat's Method). Pandy test, positive. Lange curve 2443333200. Wassermann and Kahn reactions, negative both in blood and cerebrospinal fluid.

Blood: Hæmoglobin 82 per cent; red corpuscles 4·1 million; reticulocytes 4·5 per cent.; white cells 12,900; polymorphs 70·5 per cent.; eosinophils 3·5 per cent.; basophils 2 seen in 600 cells; lymphocytes 24 per cent.; hyalines 2 per cent. Platelets 80,000, rising to 130,000 in four days, when they remained approximately constant. Clotting time, seventy seconds; bleeding time, three minutes twenty seconds.

Serum proteins: 5·35 per cent. (albumin 3·65 per cent.; globulin, 1·69 per cent.) Blood chlorides, 0·68 per cent. No abnormal capillary fragility by the venous compression test.

H. M. Sinclair, of Oxford, kindly estimated the apparent concentration of vitamin B_1 in the blood and found it to be within normal limits.

Urine: Ascorbic acid output, 3·0 mg. *per diem.*

During the eight weeks between his admission and his death, his diarrhœa was rather intermittent, and during the periods of the watery diarrhœa he became very exhausted. At no time was pus or blood seen in the stools, nor did he have any colic. His œdema varied, but it was never gross. He had no enlargement of the liver or congestion of the veins of his neck till terminally.

He was put on a light residue-free diet and his appetite remained good.

A tentative diagnosis was made of beri-beri, due to failure to absorb vitamin B_1 owing to a chronic enteritis. He was therefore treated by daily intravenous injections of 100 mg. of pure synthetic crystalline vitamin B_1.[1] Though he stated that this reduced his weakness, no improvement was demonstrable objectively. His heart remained of the same size, and, apart from some slight improvement in the electrocardiogram, there was little change in his condition.

He suffered from a mild influenzal attack in the fourth week of his stay, from which he recovered rapidly. But in the seventh week he developed a sore throat, during a ward epidemic, and hæmolytic streptococci were found in swabs from his tonsils. His diarrhœa became rapidly worse, leading to incontinence. More marked signs of cardiac failure appeared. Finally, he became rapidly more dyspnœic and cyanosed and died in about an hour from the onset of these more severe cardiac manifestations. Apart from these two infections he was apyrexial.

AUTOPSY FINDINGS.

P.M. No. 118/37. The autopsy was performed twenty-four hours after death, the body having been kept in a refrigerated mortuary. The body was of medium build, showing wasting of the muscles and little subcutaneous fat. There was no œdema of the legs, but some over the lumbar region. There were numerous petechiæ on the limbs and trunk.

Cardiovascular system.—The pericardial sac was normal. The heart weighed 750 grm. and was considerably enlarged on both sides. The myocardium was uniformly pale, double the normal thickness, firmer than normal in consistency and showed loss of muscular texture. The columnæ carneæ and papillary muscles were hypertrophied. The chambers were dilated and contained a little post-mortem clot. Apart from slight atheroma of the aortic cusp of the mitral valve, which extended to the aortic ring, there was no endocardial or valvular abnormality. The coronary arteries were normal. The aorta showed a little superficial fatty atheroma in streaks and was smaller than normal for the man's size, both in the diameter of its lumen and the thickness of its wall. The pulmonary artery and venæ cavæ were normal.

Respiratory system: The pleural cavities each contained 250 c.c. of slightly blood-stained fluid. There were a few sub-pleural petechiæ at the left base.

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[1] Kindly supplied through Professor Peters, of Oxford, by Messrs. Bayer and Messrs. Hoffmann-La Roche.

The lungs were moderately emphysematous but partially compressed, though air-containing throughout. The right and left lungs weighed 775 and 700 grm. respectively.

Alimentary system : The stomach was greatly distended with gas and bile-stained fluid, but the mucous membrane appeared normal. The first metre or so of jejunum was distended, and beyond that point some 30 cm. of jejunum were hæmorrhagic, with thickened œdematous walls and dark-red necrotic mucous membrane. This portion was infarcted. The intestinal tract beyond this point was of normal diameter, though the walls were thickened and firm in consistency. The mucous membrane showed numerous hæmatomata, varying in size, from a few mm. to 1 cm. in diameter. These were particularly numerous in the pelvic colon. The peritoneal cavity contained 2 litres of blood-stained cloudy fluid, which in the pelvis was purulent. The peritoneum throughout showed a fibrino-purulent exudate of recent origin which was hæmorrhagic in the region of the infarcted jejunum. The liver weighed 1,650 grm. and was slightly enlarged, pale and firm in consistency. Gall-bladder, biliary tracts and pancreas normal.

Lymphatic system : The spleen weighed 250 grm., was twice the normal size with smooth surface and uniformly pale, but with firm pulp in which the Malpighian follicles were obscured.

Urinary system : The kidneys each weighed 125 grm. and were normal in size, pale with finely scarred surfaces and moderately adherent capsules. The cortices showed slight contraction and irregularity at the periphery, but the rest of the parenchyma was normal. The pelvis of the right ureter showed a large submucous hæmorrhage. The bladder was normal except for submucous petechias in the region of the trigone. Bilateral hydroceles each containing 100 c.c. of clear fluid were present. The prostate was normal and the testes were uniformly enlarged.

Endocrine system : the right and left suprarenal glands weighed 15 and 10 grm. respectively. (Normal weights=8 to 10 grm.) The pattern was normal. The thyroid was normal.

Nervous system : The meninges, brain, and spinal cord appeared normal, but all the posterior root ganglia were enlarged to approximately double the normal size. The right ulnar, peroneal and sciatic nerves were similarly enlarged throughout their courses and firmer than normal in consistency.

Iodine test : It was not until the tissues were examined histologically that amyloid disease was discovered and the test was done on the heart, liver, spleen, and kidneys, which had been fixed in formalin. The test was slightly positive in the heart, spleen and kidneys, but negative in the liver. In the heart the characteristic dark brown colour was noticeable in the epicardium and in the sub-endocardial tissue, while in the kidney it was confined to the medulla.

HISTOLOGICAL EXAMINATION.

General remarks : Sections were taken of the heart, voluntary muscle, lungs, intestines, liver, pancreas, spleen, abdominal lymph-glands, kidneys, thyroid, suprarenal glands, testes, brain, spinal cord, posterior root ganglia and peripheral nerves. The following stains were employed: hæmatoxylin and eosin, Van Gieson's and Weigert's stains for fibrous and elastic tissues respectively, methyl violet, methyl green, and Congo red for amyloid, Marchi's method for nerve tissue, and osmic acid for fat.

With hæmatoxylin and eosin the amyloid was represented as a homogeneous substance, bright pink in colour, of glassy appearance and devoid of structure. When freshly stained, methyl violet, methyl green and Congo red confirmed the presence of amyloid, though methyl green was the most successful of the special stains. The amyloid was present in all the tissues examined with the exception of the brain and spinal cord.

Heart: The auricles were more severely affected than the ventricles, and this was probably due to the relatively greater amount of connective tissue in the former. Both the auricles showed numerous nodular deposits, fairly uniform in size, in the epicardial and sub-endocardial tissues and in the vicinity of the vessels in the myocardium. In addition, all the small arterioles and arteries showed more or less complete replacement of the media and adventitia by amyloid. The muscle fibres were considerably atrophied and showed loss of striation and pyknosis and kariolysis in the nuclei. There appeared to be more amyloid than parenchyma and connective tissue combined. In the ventricles the amyloid was evenly distributed through the inter-fascicular connective tissue, epicardium, and sub-endocardium and the walls of the smaller arteries and arterioles. The muscle cells were markedly atrophic.

Voluntary muscles: Sections were taken from the pectoral and calf regions and showed only slight infiltration of the arterioles and perivascular connective tissues with amyloid.

Nervous system: The brain and spinal cord were unaffected with the exception of the choroid plexus, which showed a perivascular infiltration of amyloid, particularly around the arterioles and capillaries. The dura of the cord, however, showed an occasional minute deposit of amyloid. The posterior root and sympathetic ganglia from the cervical, thoracic and lumbar regions, but particularly the last, showed severe amyloid disease. The fatty connective tissue which surrounds the ganglia showed a delicate reticulum of amyloid lying between and accentuating the outlines of the fat cells, while numerous small deposits were present in the walls of the arteries. The most striking change was inside the ganglia, which contained numerous nodules scattered diffusely in the interstices between the ganglion cells and axis cylinders. The ganglion cells were surrounded by masses of amyloid (fig. 2). Their cytoplasm was coarsely granular and vacuolated and their outline was indented and irregular. Many of the ganglion cells were diminished in size, and appeared compressed by the amyloid, while the course of the axis cylinders was distorted. The ulnar, sciatic, and peroneal nerves were similarly affected. The connective tissue sheaths of the nerve bundles and particularly the perineurium were irregularly thickened by numerous oval or rounded nodular deposits (fig. 3), while individual nerve fibrils appeared compressed and deviated by similar

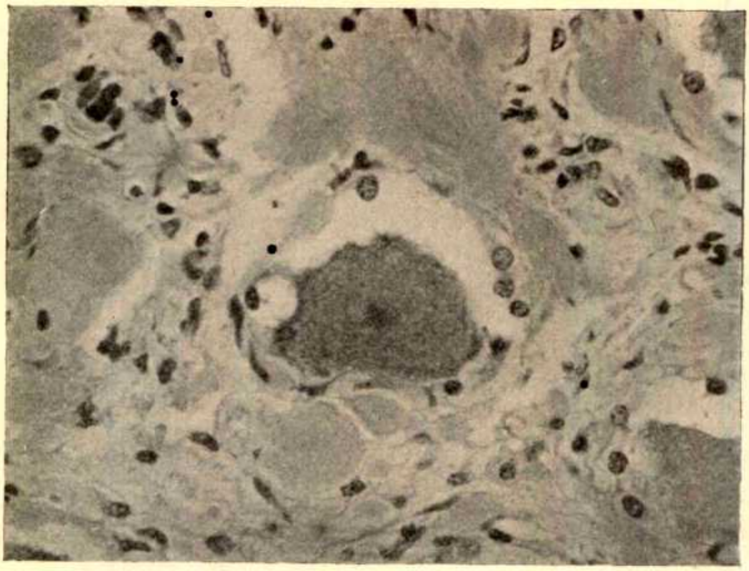

FIG. 2.—Photomicrograph of posterior root ganglion showing atrophy of a ganglion cell which is surrounded by amyloid. H. and E. × 410.

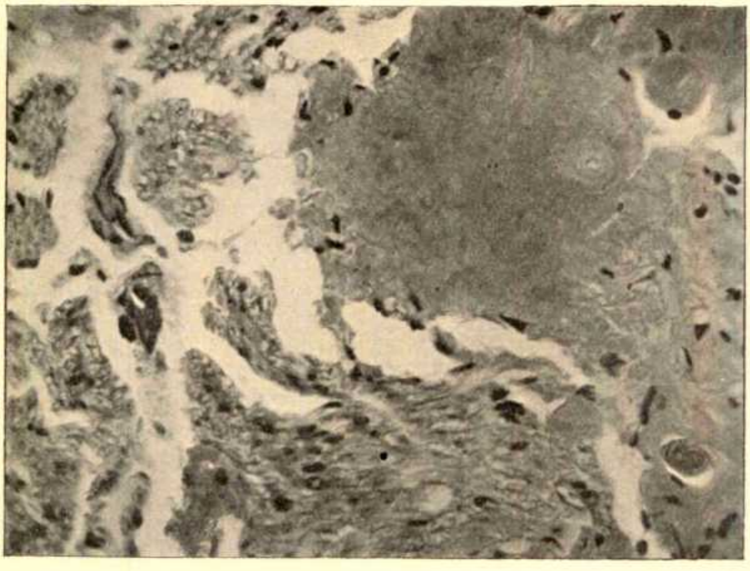

FIG. 3.—Photomicrograph of sciatic nerve showing amyloid infiltration of the connective tissue. H. and E. × 340.

deposits. In addition there was a diffuse delicate infiltration of the connective tissue of the nerve by amyloid deposits, which radiated from the arteries, whose media and adventitia were uniformly infiltrated.

Alimentary system: The small and large intestine showed diffuse amyloid deposits in the submucosa, which extended into the intestinal villi and caused them to become distended and separated from one another, and from the underlying muscle. The arteries and the veins showed severe medial deposits of amyloid, which extended into the connective tissue of the mesentery. No occlusion of the mesenteric vessels was found to account for the infarction of the loop of jejunum, but the amyloid infiltration of the arteries and veins was particularly severe in this region.

Hepatic system: The liver was scantily affected: the amyloid was confined to the small hepatic arteries and the connective tissue of the portal areas. The parenchyma was normal.

Lymphatic system: The spleen showed a diffuse amyloid infiltration of the trabeculæ and small arteries, but no nodular deposits like those present in "sago spleen" were present. The mesenteric lymph-glands showed amyloid infiltration of the capsules and peripheral sinuses only.

Respiratory system: The lung showed minute deposits of amyloid in the arterioles and in the bronchial muscle only.

Endocrine system: The thyroid, suprarenal glands and testes showed both diffuse and nodular deposits of amyloid throughout the vessels and connective tissue, which had caused considerable compression and atrophy of the parenchyma, particularly in the testes, where spermatogenesis was absent.

COMMENTARY.

Cardiac failure.—In the absence of hyperplastic or hyaline arteriolar changes indicative of hypertension, and in the presence of extensive amyloid infiltration of the heart muscle, the great increase in weight of the heart is referable to the bulk of amyloid. This is well supported by the clinical picture in which symmetrical enlargement of both sides of the heart, the gallop rhythm, the E.C.G. changes, all pointed to a pure muscular failure. The cause of this failure appears to be atrophy of the muscle fibres due to surrounding amyloid rather than to ischæmia, from narrowing of the coronary arterioles.

Alimentary system.—Though, as in most reported cases, diarrhœa is an outstanding gastro-intestinal symptom, constipation has been reported in a few. The diarrhœa is associated in this case with intestinal hurry and not with any derangement of digestion or absorption of fat.

Muscular System.—In contrast to the cardiac muscle, the weakness of voluntary muscles is to be attributed to changes in the nerves. The pectoral and gastrocnemius muscles were free from amyloid, though clinically weak and wasted. Unlike the case described by Parkes-Weber and others (1937), there was no evidence of arterial obstruction, clinically or pathologically.

Nervous system.—The difficulty in micturition, impotence, and pupillary changes, can be explained by the infiltration of the autonomic nervous system.

ABSTRACTS OF SIMILAR CASES FROM THE LITERATURE.

(1) The case described by De Bruyn and Stern, the pathological material from which we have been able to inspect, presents very similar features to our own. This was diagnosed as a case of hypertrophic polyneuritis of Dejerine and Sotta at the time.

A carpenter, aged 52, complained of progressive weakness with pains and numbness in the arms and legs, diarrhœa and attacks of faintness and unconsciousness. This began three years before his admission to hospital. His only previous illness had been pneumonia as a child. He was married, with two healthy children. Two brothers and one sister had died with exactly similar symptoms, weakness, diarrhœa and heart failure being the outstanding features of their terminal illnesses. In each case the symptoms lasted about three years before death.

In spite of his complaint of numbness in arms and legs, sensory changes were demonstrable only in the legs below the knees, where light touch was lost. Marked general muscular wasting was present, especially centrifugally. Coarse fibrillation was occasionally seen in both quadriceps regions. Some peripheral nerves, e.g. the ulnars and external popliteals, were readily palpable. The pupils were small and reacted poorly to light, but well on accommodation. The heart sounds were feeble, blood-pressure 95/60, and a slight secondary anæmia was present. There was hypochlorhydria. The mode of death is not described, nor is the morbid anatomy of parts other than the central nervous system.

Careful clinical extracts of many cases which had macroglossia are given in the paper by Parkes Weber and others. Of these, the following had some of the clinical features of our case.

(2) Konigstein's Case (1925). Male, aged 60, had difficulty in swallowing, macroglossia, weakness in the arms, a gradual cachexia and a nodular dermatosis. Extensive amyloid deposits were found in the whole alimentary canal at autopsy.

(3) Lubarsch's Case (1929). Male, aged 54, had an eight year's history of paralysis in various groups of muscles and digestive disturbance.

(4) Mollow and Lebell's Case (1912). Male, aged 60. Complained of abdominal pains, constipation, and enlargement of the tongue. He had trouble in walking and hypertonicity of skeletal muscles. He died of cardiac weakness.

(5) Michelson and Lynch's Case (1934). Male, aged 54, had marked weakness, pain in the lumbar region and joints, macroglossia, and Bence Jones proteinurea, swollen tender fingers, bruising with very slight trauma, skin deposits, and stubborn constipation.

Two other cases are described by Perla and Gross (1935), but not summarized by Parkes Weber.

(6) Female, aged 16. Had weakness, dyspnœa and palpitations. Her joints were sometimes red, but she had no fever. Blood-pressure 124/60. The liver was felt 4 cm. below the costal margin. Some general glandular enlargement was present. Red cells, 2·5 million; hæmoglobin, 47 per cent.; white count, normal; blood-urea, 69·2 mg. per cent., and poor urea concentration. Uræmia and chronic nephritis diagnosed. She had attacks of epistaxis and purpura in the arms, with occasional convulsions. Her blood-pressure rose to 180/94, gallop rhythm, and a pericardial rub developed terminally.

(7) Female, aged 63. Had asthenia, constipation and anorexia for two years, and then developed repeated attacks of diarrhœa with watery and bloody motions. She developed pleural effusions which were repeatedly tapped. Progressive azotæmia occurred, with vomiting and anasarca. Finally, auricular fibrillation followed an impure flutter, and she died suddenly.

(8) Larsen (1930) gives a brief clinical history of a case, male, aged 65, negro, in whom cardiac failure and œdema were the main features. He had auricular fibrillation, and the comment is made that his reflexes were sluggish or absent.

Pathological Discussion.

Primary amyloid disease has been classified by Lubarsch on an anatomical basis into three main groups:—

(1) The first is said to be characterized by involvement of tissues of mesodermal origin, such as the cardiovascular, gastro-intestinal and voluntary muscle, which show a tendency to develop nodular deposits, while the organs usually affected in the secondary form remain comparatively free.

(2) A second "tumour-forming" type consists of small, solitary or

multiple "tumours" of amyloid occurring in the eye, bladder, urethra, pharynx, tongue, skin, or in the respiratory tract.

(3) A third well-defined group appears to be associated with multiple myelomata.

The present case approximates to the first type of Lubarsch, but it also illustrates the considerable overlapping which may occur between his types. The small arteries throughout the body with the exception of those in the brain and spinal cord were affected in varying degrees, least in the lungs and liver, and most in the heart, gastro-intestinal and endocrine systems. The degree of local destruction of the parenchyma varied correspondingly.

It is generally accepted that amyloid disease begins in the small arteries and arterioles and spreads in continuity to the connective tissue, where its deposition may cause atrophy of the adjacent parenchyma, whether by pressure or vascular disturbance it has not been possible to determine. It appears to remain extra-cellular.

The origin of amyloid in both the primary and secondary forms of amyloid disease is still unknown. Chemical analysis of dried materials has been done by Eppinger (1922), who found that amyloid contained no sulphur, phosphorus or carbohydrate, but that purines and diamino acids constituted the greater part. However, the variable staining properties of amyloid point to a variability in its chemical composition, and what is recognized as amyloid histologically probably comprises a group of closely-allied substances. The amyloid in the present case exhibited the usual histological features and stained characteristically with the usual stains.

Alteration in the blood proteins, such as diminution in total serum protein, and reversal of the albumin-globulin ratio, have been described by Humphreys (1934), and has led Perla and Gross to suggest some derangement of protein metabolism as a possible cause. Since the alterations in the serum proteins may well have been due to the accompanying renal disease in the cases described, and is far from being an invariable feature of generalized amyloid, the suggestion has little to support it.

SUMMARY.

(1) A case of primary generalized amyloid disease with involvement of the nerves is described.

(2) The muscular weakness which was a conspicuous feature of this case is attributed to amyloid infiltrations of the nerves.

(3) Attention is drawn to a clinical syndrome of muscular weakness, myocardial failure and alimentary disturbance, which is common to this case and to eight others abstracted from the literature.

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NOTICES OF RECENT PUBLICATIONS.

Neuro-ophthalmology. By R. LINDSAY REA. London: William Heinemann (Medical Books), Ltd. 1938. Pp. 568. Price 42s.

The author has written an exhaustive account of the ophthalmic aspect and associations of diseases of the nervous system, including under the latter heading the psychoneuroses. The task is necessarily an ambitious one for the ophthalmic surgeon, for it covers a wide range of pathological and clinical knowledge, with much of which he can have little but a literary acquaintance.

The chief difficulty, perhaps, which besets an author in these circumstances is that of assessing the value and significance of all that part of his subject with which he has not a first-hand clinical experience. The critical faculty cannot adequately do its work where this experience fails. Here and there in the present book is evidence of this difficulty, shown as statements and judgments that the experienced neurologist would not have made. Thus disseminated sclerosis is baldly classed with tabes dorsalis as "infections of the nervous system," a statement which is later qualified. The optic atrophy of tabes is said "often" to precede other signs of this malady. Nystagmus is said to be "commonly" present in subacute combined degeneration of the cord, and the discovery of the association of this malady with pernicious anæmia is attributed to a modern source very many years later than it was actually made. Finally, it is premature to say that "progress has reached the stage when the location of tumours of the brain may be discovered by the electro-encephalogram."

Very many nervous diseases which have no significant ophthalmological signs are given scrappy paragraphs, too brief to be of value and lacking the balance and accuracy that are necessary to gain the reader's confidence.

The chapter dealing with the psychoneuroses attempts within a page or two to discuss the various hypotheses which compete for acceptance as to the genesis of these disorders, a topic not within the compass of the book's title, and not adding to its value.

These few examples will serve to indicate that the author has perhaps cast his net too wide, and would better have served his readers had he been more modest in his aims.

Nevertheless, on the more strictly ophthalmological side of the book, he writes clearly and with authority and has provided the ophthalmologist with a useful compilation of the neurology of the eye.

The book is excellently produced, has an exhaustive bibliography, and is well illustrated.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By F. R. FORD. London: Baillière, Tindall and Cox. 1937. Pp. 953. Price 38s.

No more comprehensive or valuable addition to the ranks of neurological textbooks than Dr. Ford's has appeared in the English language for some considerable time. It forms a work of reference without which no neurologist's library will be complete. It includes succinct and extremely clear sections upon every recorded affection of the neuromuscular system within the age period with which it deals. These accounts are admirably balanced, and each section is followed by an adequate and representative bibliography.

It opens with the usual chapters upon clinical methods of examination and upon the essentials of nervous anatomy and physiology. The classification is unusual but practical, and consists of chapters on prenatal diseases, heredo-familial and congenital diseases, infections and parasitic diseases, toxic and metabolic disorders, vascular and circulatory disorders, neoplasms, injuries, diseases of the autonomic system, muscular diseases, and a final chapter devoted to symptom-complexes.

The illustrations and diagrams are original, well chosen and well produced.

The book really deals with more than diseases peculiar to the pre-adult period of life and it is in fact a textbook of neurology. A series of typical case reports illustrate the various conditions described. It is to be hoped that in future editions the index may be improved. It is incomplete and contains numerous misspellings.

Die Kuppelungen von Pupillenstörungen mit Aufhebung der Sehnenreflexe. By VON F. KEHRER. Leipzig: Georg Thieme. 1937. S.60. Price 6M.

The author reviews in some detail all the published works on the subject of the tonic pupil, gives minute descriptions and classifications of the clinical variants, and of the pupillary anomalies that may have to be differentiated from the syndrome he is dealing with.

The monograph is mainly descriptive and no fresh generalizations emerge, but it is a useful résumé of the present state of knowledge upon its subject. Several important papers that are freely referred to in the text find no place in the bibliography, and no reference is given to the journals in which they appeared.

Children Handicapped by Cerebral Palsy: Psychological factors in management. By ELIZABETH E. LORD, with a medical explanation by B. CROTHERS. New York: The Commonwealth Fund. London: Oxford University Press. 1937. Pp. 102. Price 5s. 6d.

This valuable little book deals with the care, management and training of a class of chronic sufferers for whom in the past little beyond crude orthopædic procedures have been attempted. It should be studied by all who may have to advise upon the training of the diplegic child, by all who may have to undertake or supervise this training, and there are some mothers into whose hands it might be put with advantage.

The assessment of mental and physical condition and potentialities is described, and its bearing upon the plan of treatment to be adopted. This plan embraces the various aspects of the child's training and education, and due stress is laid upon the necessity of trying to make the situation to be dealt with clear to the child's parents, and of securing, when possible, their intelligent co-operation.

Neurology. By R. GRINKER. Second Edition. London: Baillière, Tindall and Cox. 1937. Pp. 1,000. Price 38s.

In the preface to this edition the author refers to the difficulty of avoiding the progressive enlargement of a textbook, and to the changes involved in deleting matter that has not stood the test of time since the appearance of the first edition.

To-day, perhaps, the chief art in the writing of a textbook is not in the inclusion of all that has been said on its subject, but in the exclusion of what has not in some measure already stood the test of time. A textbook is scarcely the place in which the merely hypothetical or the uncorroborated should appear. For these the original paper and the critical review are the appropriate media.

Difficulties must also beset the endeavour to do justice to recent advances and changes of opinion in anatomy and physiology as well as to clinical neurology and neuropathology within the bounds of a single volume, and the attempt to do so often leads to an overloading with the former at the expense of the latter. Thus the proportions desirable in a work for clinicians are lost.

In the present edition just over a quarter of the matter is devoted to anatomy and physiology, including recent additions to knowledge that have yet to find a clinical application, or indeed any application to the human subject. Approximately twice as much space is given to the anatomy and physiology of the cerebellum as to its diseases and their symptoms and pathology, while the cyto-architectonics of the cerebral cortex occupy as many pages as are devoted to multiple peripheral neuritis. Indeed, the purely clinical sections of the book are not on the same scale of comprehensiveness as those given to the ancillary sciences.

In the matter of clinical description, such a progressive malady of the nervous system as disseminated sclerosis, for example, may be regarded as a sequence of events, this sequence being the natural history of the malady. To obtain the story of his illness from the patient, and to assess the significance of his symptoms and physical signs demand of the investigator a knowledge of this natural history, and it is one of the first functions of a textbook to provide this. Mere disjointed paragraphs describing—in no matter what detail—the separate components of the clinical picture do not give this vivid sense of an active process.

To provide such a continuous story undoubtedly calls for a ripe clinical experience and a modest measure of literary skill, but it is the vivid accounts of disease given by the authors of a past generation—as those acquainted with Gowers' famous textbook will acknowledge—that made their books, and still make them, so full of life and so delightful to read. Without this element no textbook can hope to reach the first rank.

In the independence and freshness of his thought and the clarity of his expression the author has shown his ability to provide this, and it may be hoped that in the further editions of his work that will be called for, he may find it expedient to alter somewhat the balance of his material. The first approach of the clinician to nervous disease is by simple observation at the bedside and the fullest aids to this should be given him. If economies of space are called for, they should not be made at the expense of clinical medicine.

With these reservations, the book may be recommended to the student of neurology as a lucid exposition of modern neurological knowledge.

JUNE, 1938

BRAIN.

PART 2, VOL. 61.

SOME OBSERVATIONS ON HEADACHE.

BY D. W. C. NORTHFIELD.

(*From the Department of Neuro-Surgery of the London Hospital.*)

HEADACHE is an exceedingly common complaint from which most persons have suffered. In spite of, or perhaps by reason of, its occurrence as a symptom of disease in various parts of the body, the mechanism of its production remains obscure. Such a problem is most likely to be solved by the detailed study of a small group of cases. In this discourse, the study of headache will be limited almost entirely to cases of intracranial tumour, which form a subject conspicuously favourable for clinical research. The lesion is unequivocal and is frequently amenable to operative removal. The investigation of the patient and subsequent operation under local anæsthesia provide many opportunities for the experimental production of headache.

CLINICAL FEATURES.

Although many persons have difficulty in expressing adequately the discomforts and pains they experience, the headache due to a space occupying intracranial lesion is truly one of pain or intense discomfort. It is frequently described as a dull or throbbing ache, a bursting, burning, or sharp stabbing pain, the patient often giving some graphic comparison, such as " it is like a vice closing on my temples " or " it is like something opening and shutting in my head." The pain is usually referred vaguely to the interior of the skull across the forehead, through the temples, or in the occipital region. It may be quite generalized, or may affect only one side, and during the course of the illness it may shift from one area to

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[1] This paper formed the basis of a Hunterian Lecture delivered at the Royal College of Surgeons on February 10, 1937. The work has been performed during the tenure of the Will Edmonds Clinical Research Fellowship.

another. In patients in whom the tumour arises in the posterior cranial fossa the complaint of pain and stiffness in the muscles of the neck is particularly common, and this symptom tends also to develop sooner or later if the tumour be situated in other parts of the skull.

There are interesting details concerning the time of onset of headache, and factors which cause its aggravation. It has a predilection for occurring in the morning, usually immediately the patient wakes, but it often wakens him at an unusually early hour. Rising from bed makes it much worse, or the change in posture may bring on the headache if it is not already present. The majority of patients choose to lie in bed with the head only slightly raised and only a few prefer to sit bolt upright. In all cases it is the sudden *change* of posture which seems to be resented. Movement of the head on the neck is liable to increase or precipitate a headache, and this is especially noticeable when the pain is in the back of the head. In such a case examination will usually demonstrate tenderness and spasm of the suboccipital muscles.

One variety of headache may occur which I believe to be pathognomonic of intracranial tumour. This pain is generalized, paroxysmal, and apparently agonizing, causing the patient to writhe and to scream, and to hold his head in his hands. He becomes unco-operative and is deaf to the observer's questions. Indeed, this type of headache not infrequently ends in semiconsciousness, and there may be amnesia of the attack. I choose the term paroxysm deliberately, for the spasm of pain comes on quite suddenly in a patient previously free from headache, and in the course of a second or so attains its maximum intensity. It may last from thirty seconds up to half an hour and then may disappear as quickly as it came, leaving the patient exhausted.

Such a headache, especially when associated with semiconsciousness, is usually confined to the terminal stages of the disease, when it may recur several times in the day. Indeed, its presence should be viewed with alarm, for it indicates a state in which the patient may die, either suddenly or after passing into coma. The urgency of this dangerous state cannot be over emphasized, and this point is well illustrated in the following case, in which the paroxysm of headache ended in an epileptiform attack.

A man, aged 34, had had slight headaches for three years, which had become much more severe in the last six months, and were situated all over the head. After admission to hospital the attacks of headache increased in frequency, and ultimately six occurred in five hours, three within a period of ten minutes. Observed on one occasion, the headache appeared to be paroxysmal, exacerbations every minute causing him to rub his head and to cry out "My head! my head!" Squirming movements of the limbs were present, with a tendency to adversive rotation of the body to the left. In one of the terminal attacks there was most intense headache, a complaint of vertigo—when he nearly fell out of bed in attempting to compensate for it—adversive movements, and semiconsciousness eventually developed. Each attack lasted about two minutes, and there was complete amnesia for it.

In consequence of the very frequent recurrence of these headaches operation was immediately performed. The intraventricular pressure was over 600 mm. and the dura mater stony hard. A tumour was disclosed situated in the right parietal lobe and was partially removed. The brain was under great tension and in a state of intense hyperæmia, consequently severe hæmorrhage occurred, but the patient made a satisfactory recovery.

Paroxysmal headache occurs in a wide variety of cases including such tumours as glioma of the basal ganglia, acoustic neurinoma, chordoma of the base of the skull, suprasellar cyst, hæmangioma of the cerebellum and colloid cyst of the 3rd ventricle. Only in these rare benign tumours of the 3rd ventricle is paroxysmal headache observed sufficiently frequently to constitute an item of evidence for correct localisation.

What is the chronological incidence of headache in intracranial tumour? Of 100 unselected case records of verified tumours in the London Hospital, in 36 headache was the initial symptom, or it developed at the same time as other complaints (Chart 1). This figure corresponds closely with that of Dowman and Smith (1928). Further analysis is illuminating. In the 100 cases, there were 9 acoustic tumours and in none of these was headache the first symptom. But in 12 other cases of posterior fossa tumour, mainly cerebellar gliomas and hæmangiomas, headache was the first symptom in 10. There were 37 gliomas of the cerebral hemisphere, and in 13 headache was the first symptom, and it is noteworthy that the proportion was approximately the same for meningiomas, 5 out of 14. Considerable discrepancy was found between the incidence of headache as the first symptom in temporal lobe and in frontal lobe tumours. Whereas in temporal tumours headache was the first symptom in 7 out of 17 cases, in frontal tumours it was the first symptom in only 8 out of 28

CHART 1.

THE INCIDENCE OF HEADACHE AS THE INITIAL SYMPTOM IN CASES OF VERIFIED INTRACRANIAL TUMOUR

in 36 out of 100 unselected cases ... ... = 36 per cent.
in 0 out of 9 cases of acoustic neurinoma ... ... = 0 per cent.
in 10 out of 12 other cases of posterior fossa tumour = 83 per cent.
in 13 out of 37 cases of cerebral glioma ... ... = 35 per cent.
in 5 out of 14 cases of cerebral meningioma ... = 36 per cent.
in 8 out of 28 cases of frontal lobe tumour ... ... = 29 per cent.
in 7 out of 17 cases of temporal lobe tumour ... = 41 per cent.

cases. From ventriculography, we know that temporal tumours cause considerable displacement of the 3rd ventricle, and are very liable to produce hydrocephalus. If these figures are large enough to have statistical value, it is clear that headache is likely to precede other symptoms in those cases in which the tumour, by reason of its location, tends to impede the flow of cerebrospinal fluid through the ventricular system. In an acoustic tumour, however, because of its intimate relation to certain cranial nerves, focal signs will precede headache.

Headache is nearly always referred to the forehead, whether or not it involves other areas as well (Chart 2). It is worth noting that out of a total of 121 cases excluding pituitary adenomas, frontal headache was absent in only 5 per cent. of cases of supratentorial tumour, as compared with 25 per cent. where the tumour was infratentorial. Pain in the neck was present in 22 per cent. of supratentorial tumours and in 49 per cent. of infratentorial tumours. This pain in the neck associated with muscular spasm is usually observed in its severest form when the tumour occurs low in the posterior fossa, forming a tongue which plugs the foramen magnum. A similar mechanism doubtless operates when the tumour is situated elsewhere, for the cerebellar tonsils may be herniated through the foramen magnum, at times to a level as low as the 2nd cervical vertebra. The painful muscular spasm is probably caused by the pressure of the tumour or the tonsils on the posterior roots of the upper cervical nerves.

CHART 2.

THE DISTRIBUTION OF THE PAIN

FRONTAL HEADACHE

with or without involvement of other areas was present in
95 per cent. of cases of supratentorial tumour.
75 per cent. of cases of infratentorial tumour.

PAIN IN THE NECK

with or without involvement of other areas was present in
22 per cent. of cases of supratentorial tumour.
49 per cent. of cases of infratentorial tumour.

UNILATERAL HEADACHE

Of 42 cases

in 6 the tumour was in the middle line.
in 32 the tumour was situated on the same side as the headache.

N.B.—In only 4 cases was the headache on the side opposite to the tumour.

In 42 patients the headache was entirely or predominantly unilateral and did not shift from side to side. In six of these the tumour was situated approximately in the middle line, but it is noteworthy that in only four cases was the tumour found to be on the side opposite that affected by headache. These were two cases of frontal and one of parietal meningioma, and one case of abscess of the frontal lobe.

Headache due to an adenoma of the pituitary gland is of a special type. It is frequently more severe in acromegaly, though it never becomes a paroxysm of agony. The pain may be merely a dull ache, or actually throbbing over the forehead and through the temple. Rarely it may spread to the occiput. In contrast to the headache resulting from other tumours, it is frequently associated with, or replaced by, pains described as neuralgia, related to one or both eyes, in the eyebrow, or in some portion of the face. This pain does not progressively involve larger areas of skin supplied by the trigeminal nerve, as with a tumour of the middle cranial fossa or of the Gasserian ganglion, or with large aneurysms of the internal carotid artery.

The Intracranial Pressure During Headache.

It is commonly accepted that the headache produced by an intracranial tumour is due to the increase in the intracranial tension. When the patient is resting horizontally in the lateral position, the pressure of the cerebrospinal fluid in the lumbar theca is identical with the pressure in the ventricles. Of a series of 102 verified cases of tumour, in 63 the pressures exceeded the normal of 100 to 200 mm. of fluid. The highest was an intraventricular pressure exceeding 700 mm., during gas, oxygen and ether anæsthesia. Ether, even in small proportions elevates the pressure slightly, but this was amply offset by the loss of fluid while the manometer was being connected to the needle. The cases which appear to me vitally important to the subject under discussion, are those in which the pressure was not raised. In 39 the pressure was less than 200 mm., and in 16 it was actually *below* 100 mm. Many of these cases with normal or subnormal pressures had been experiencing very severe headache during the period immediately prior to the investigation. In many patients however, headache may be absent although the intracranial pressure is very high. It will be instructive to consider some of these cases in detail (Chart 3). In each, the operation was performed under a local anæsthetic.

Many more similar observations could be mentioned, but these are sufficient to demonstrate that the absolute value of the intracranial pressure bears no relation to the presence or absence of headache. Although headache is clearly related to those diseases which induce an increase in the intracranial pressure, the high pressure in itself is probably not the cause of the headache. I hope later to prove that headache readily occurs as a result of any sudden *alteration* of pressure, whether an increase or a decrease.

CHART 3.

THE RELATION BETWEEN HEADACHE AND INTRACRANIAL PRESSURE

Of 102 cases of verified intracranial tumour
in 63 cases the pressure exceeded 200 mm.
in 39 cases the pressure was less than 200 mm.
in 16 cases the pressure was less than 100 mm.

Case	*Headache*	*Pressure*
1	severe	low
2	severe	low
3	absent	high
4	absent	high
5	absent	high
	severe	low
6	absent	high
	severe	high

(1) A patient with a tuberculoma of the cerebellum suffered from severe bouts of headache and pain in the neck. At operation the ventricular pressure was so low that the fluid did not rise to the mouth of the needle.

(2) In a patient with a cystic glioma of the frontal lobe, four paroxysms of headache occurred a few hours before the ventricles were tapped ; the ventricular pressure was only 40 mm.

(3) A patient with severe chronic hydrocephalus had been perfectly free from headache during the week immediately preceding ventriculography at which the pressure was 600 mm.

(4) In a patient with a frontal meningioma, and who was experiencing no headache at the time, the ventricular pressure was 400 mm.

(5) In a patient with a cerebellar glioma, the ventricular pressure at the beginning of the operation was 430 mm., when he had no headache. Later in the operation he complained of severe headache, but the pressure was zero.

(6) The pressure was over 300 mm. in a patient with a colloid cyst of the third ventricle, during a period of freedom from headache. Five years later, after a long interval of well-being, when headache was severe, the pressure was still over 300 mm.

Such considerations as these cast doubt upon the commonly accepted views that the headache of a brain tumour arises from stimulation of the dura mater by the increased intracranial pressure. The following cases offer further support for this attitude.

A man, aged 32 years, was first admitted to hospital in November, 1932. He had suffered from headaches for four years ; they started in the back of the neck, spreading forward around the temples and settling in the middle of the forehead, occurring regularly in the morning on getting out of bed. For eleven months there had been epileptiform seizures of a generalized type. Papillœdema and localizing neurological signs were absent. In the radiogram of the skull could be detected a small area of pathological calcification in the right temporal lobe; encephalography revealed undilated ventricles, the right lateral ventricle was a little narrower than the left and the system was slightly displaced to the left.

A diagnosis of calcified glioma of the right temporal lobe was made, luminal was prescribed, and the patient was kept under observation.

In June, 1934, the patient developed neuralgic pains in the right side of the face. The headaches gradually became confined to the right forehead and temple, but he averred that they were not nearly so frequent, nor did they last so long. He was found to have papillœdema of 1·5 D. Fresh radiograms of the skull showed a striking contrast with the earlier ones: there were now marked indications of increased intracranial pressure—thinning of the temporal squame on the right side, erosion of the sella turcica and increase in the diploë; the area of pathological calcification in the right temporal lobe had grown considerably in size. Operation was performed, and a large oligodendroglioma removed from the right temporal lobe.

It is incredible that the headaches from which this patient suffered could have been due to pressure on the dura mater. They antedated other symptoms by a period of several years, and were proved by an encephalogram to be unassociated at that time with any hydrocephalus. During the nineteen months before operation, the pressure on the dura mata was slowly increasing, as evidenced by the incontrovertible radiographic signs and by the terminal development of papillœdema; yet this headache gradually improved! The neuralgic pains in the right side of the face, although unassociated with any demonstrable loss of cutaneous sensibility, may have been due to pressure upon the Gasserian ganglion, or possibly they were referred from the dura mater of the middle cranial fossa.

A patient, aged 27 years, had suffered for two years from occipital headaches which radiated into the neck. A suboccipital decompression was performed, but the dura mater was not opened. This operation gave relief from headache for six months. Symptoms then recurred, and at a second operation a cerebellar ependymoma was removed. Although left intact at the first operation, the dura mater had gradually become stretched during the interval between the operations, so that a considerable cerebellar hernia developed.

In this case, when the dura mater was left unsupported by bone, the intracranial pressure was sufficiently high to stretch it, yet headache was relieved for a considerable time. If the dura mater were the sensitive structure responsible for headache, one would have expected that with its progressive stretching, headache would have been a conspicuous feature.

Unilateral headache cannot be adequately explained on a basis of dural stimulation by pressure. The differences in pressure within various parts of the brain when a tumour is present must be very small indeed, for the brain being so soft, is immediately displaced from an area of high pressure to one of low pressure; proof of such displacement is found at post-mortem. The following case illustrates clearly the difficulty of accepting the dura mater as the sensitive structure.

A patient had an operation for a glioma of the right frontal lobe, which subsequently recurred. The headache of which she complained was paroxysmal in type and affected only the right side of the forehead. A large cystic cavity was located in the right frontal lobe, from which yellow fluid under a low pressure could be aspirated in quantities up to three ounces; this procedure usually gave relief from headaches after a few days had elapsed. A second operation was eventually performed, when the cavity was explored and a considerable amount of tumour which was lining the anterior part of the cavity was removed. Posteriorly the cyst came into contact with the right ventricle, a septum of paper thinness separating their contents; this septum measured about 3 by 2 cm. The aim of the operation in this case was to drain the contents of the cyst into the ventricle in order to obviate repeated aspiration, and to achieve this the septum was freely opened.

The unilateral headache in this case could not have been caused by local pressure on the dura mater. Not only was the pressure within the cyst never observed to be greater than 70 mm. during a headache, but any increase of the pressure of its contents would be communicated immediately and completely to the ventricle. In this manner, the ventricular system would be maintained at the same hydrostatic pressure as the cyst. It is notable that the operation did not give the patient immediate relief from the pain, confirming the view adopted. Headache slowly subsided during the course of the succeeding few weeks.

Headache from causes other than brain tumour.

Consideration of certain conditions other than intracranial tumour suggests the possibility that headache may be vascular in origin. Patients suffering from an intracranial aneurysm often complain of recurrent headache, which commonly affects one side of the forehead more than the other. In fact, it is taught that periodic unilateral headache, which never changes from one side to the other, is more likely to be due to an aneurysm than to be migrainous. The sudden severe pain which heralds a subarachnoid hæmorrhage may be felt in or over one eye—and at the post-mortem examination the aneurysm is found in the same side of the head. This suggests that the gradual stretching of the wall of the artery and the final rupture of the aneurysm may set up a train of afferent stimuli which is interpreted as headache. The aneurysms which develop from the circle of Willis are not of sufficient size to cause an increase in the intracranial pressure. The large ones which occasionally develop from the internal carotid artery usually cause no headache, but give rise to pain in the face owing to pressure upon the neighbouring branches of the Gasserian ganglion.

In the following case it is difficult to avoid the supposition that the headache was of vascular origin, and that the interference with the blood flow consequent upon carotid ligation provoked afferent stimuli similar to those provoked by the aneurysm.

A woman, aged 41 years, suffered from right frontal headaches, and developed a right oculo-motor palsy. The diagnosis of aneurysm of the right posterior communicating artery was confirmed by arteriography, and the right internal carotid artery was ligated in the neck. Half an hour after the operation, the patient developed a dull ache in the right side of the forehead, lasting for about twelve hours. She stated that this headache was similar to that which she had previously experienced ; it was easier sitting up, but was aggravated by lying flat ; histamine had no effect upon it.

Bramwell (1932-33) records a case in which the contrary observation was made: ligation of the internal carotid for an intracranial aneurysm banished the headache of which the patient complained, before the patient left the theatre.

Headache of varying degree and distribution frequently follows an epileptic seizure, whether or not there be a demonstrable organic lesion such as a tumour or an area of cortical atrophy. The headache may be severe and is clinically very similar to that which occurs with an intracranial tumour. The following cases have been chosen in order to illustrate these points.

A patient suffering from an astrocytoma of the right frontal lobe had had epileptiform fits for three and a half years. The fits were always followed by a right frontal headache. Eighteen months before admission to hospital, headaches occurred independently of the fits. These headaches were quite similar in situation and quality to the post-epileptic ones.

Another patient had suffered from bifrontal headaches for many years. For about one year before admission to hospital he had Jacksonian epilepsy, and each fit was followed by a headache similar to his former ones. At operation a spongioblastoma multiforme of the right frontal lobe was removed.

In two patients suffering from epilepsy, encephalography demonstrated an area of cortical atrophy. In each case the post-convulsion headaches only affected that side of the head in which this atrophy was present.

Cases such as these give support to a thesis which offers a common causal mechanism for the headaches of tumour and of epilepsy.

THE EXPERIMENTAL PRODUCTION OF HEADACHE.

I.—By Stimulating Intracranial Structures.

When the opportunity has presented, observations have been made during the course of operations under local anæsthesia to determine the sensitiveness or otherwise of the various tissues encountered.

(*a*) *Dura mater.*—It has long been considered that the greater part of the dura mater is insensitive to such operative trauma as cutting, clamping, and burning, except in the immediate vicinity of the middle meningeal arteries, but the observations which follow show that this is not so.

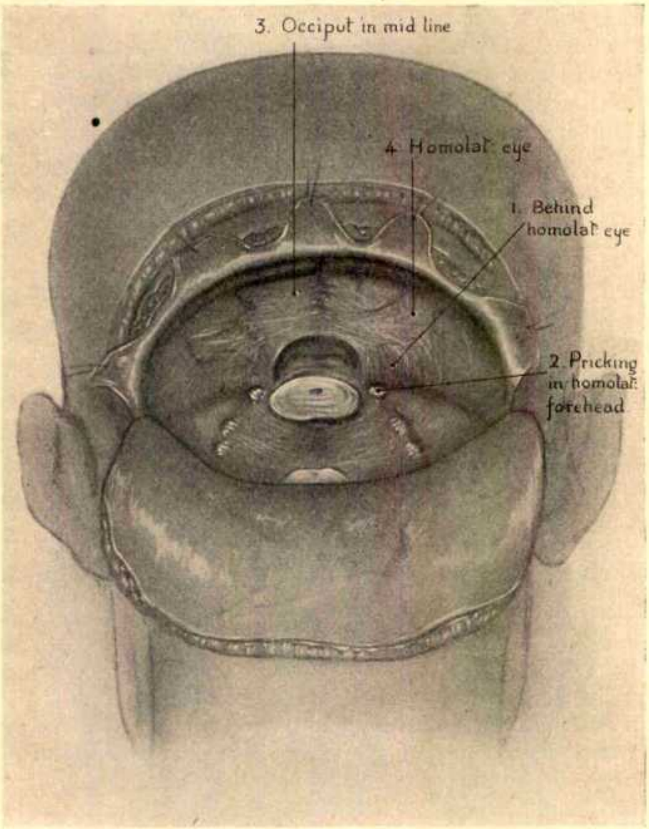

FIG. 1.

During cerebellar explorations, I have inserted an instrument under the dura mater and exerted fairly heavy traction. In each of three cases, this gave rise to an ache at the back of the head on the same side, in one case radiating into the neck.

In four cases, the inferior surface of the tentorium has been stimulated by pressure with the tips of dissecting forceps (fig. 1). At a point (1) near its free edge, 2 cm. behind the right trigeminal nerve, pain was experienced behind the right eye, somewhat less severe than the pricking pain which was felt in the forehead when the trigeminal nerve itself was touched (2). Pressure and traction (3) during the removal of a tumour caused pain in the middle of the back of the head, none in the eyes. The touch of the forceps (4) in another case caused the patient to complain of pain in the homolateral eye. When the endothermy was applied to the upper surface of the tentorium in the middle line (5) (fig. 2), or when traction was exerted on it, the patient complained bitterly of pain, but he was too unco-operative to describe its location.

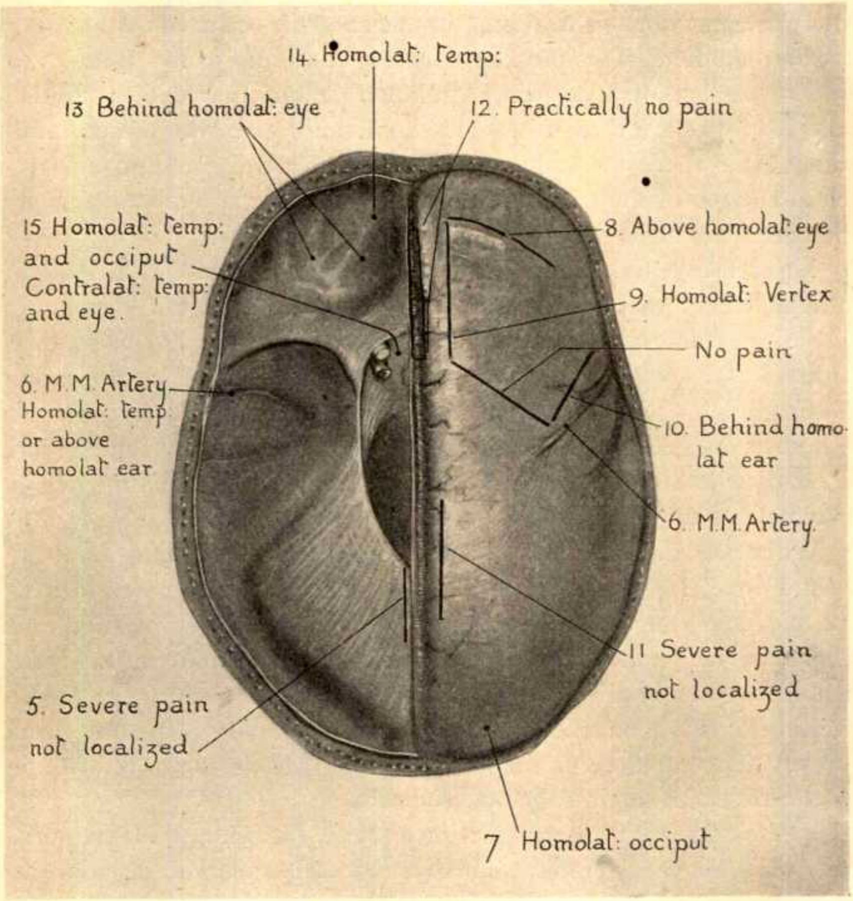

FIG. 2.

Stimulation of the middle meningeal arteries (6) either by clamping or by endothermy results usually in a fairly acute pain, referred to the homolateral side of the head, either in the temple or just above the ear. On several occasions this manœuvre has been painless.

While drilling a hole for ventriculography, in two cases there was pain in the back of the head when the dura mater in the parieto-occipital region (7) was stimulated by the perforator, the patient stating that it felt to be where the operator was working. In one case this occurred on one side and not on the other. This procedure usually causes no pain.

The passage of a de Martel guide from one burrhole to another in order to introduce a gigli saw may sometimes give rise to well localized pain. At 8 there was pain above the homolateral eye, and at 9 it was felt at the top of the head on the same side. In the temporal region (10) the pain was felt behind the homolateral ear.

The sensitiveness of the superior sagittal sinus and its neighbouring dura appears to vary considerably. In one case the use of the endothermy (11) whilst removing a meningioma caused considerable pain, but the patient was not sufficiently helpful to localize it. In another case, a portion of the sinus (12) was removed practically painlessly. In a similar study of dural pain, Penfield (1935) has frequently found this sinus quite sensitive to faradic stimulation, the pain being referred to the vertex, forehead, eye, or temple of the same side.

When the dura mater is being stripped off the orbital plate of the frontal bone (13) pain may be felt behind the inner or outer part of the eye, corresponding to the area of dura mater affected. In another case, when removing a meningioma, traction on the dura mater at many points behind the frontal air sinus (14) caused pain to be felt in the temple. By exerting traction on the diaphragma sellæ (15) in a case of pituitary tumour, pain could be produced in both temples, in the back of the head on the same side, and in the opposite eye.

In the majority of these experiments, the traction necessary to produce pain was very considerable. There was a wide range of variation in the sensibility, but the tentorium seemed to be more sensitive than other areas of the dura mater, excepting that around the middle meningeal vessels, and the dura mater lining the vault the least sensitive.

(*b*) *Cerebral arteries.*—In five patients, observations have been made on the effect of pressing upon, or displacing the internal carotid artery in the vicinity of the anterior clinoid process. In two, pain was appreciated behind or in the homolateral eye, in one the pain was referred to the temple on the same side, and in another pain was experienced in the region of the homolateral eye, not satisfactorily located, when arachnoidal adhesions were being divided close to the internal carotid artery. No sensation was experienced in the fifth case.

(*c*) *Brain tissue and walls of ventricles.*—In no case did sensation of any kind result from pressure upon the pia mater, the brain tissue or upon the walls of the ventricles. The cortical veins and arteries and the choroid plexuses were insensitive to clamping and to endothermy. In two cases, traction in certain directions upon a tumour adherent to the choroid plexus of the temporal horn gave rise to pain which was felt deep in the head near the vertex on the same side. It could not be ascertained whether the pain was due to movement of the choroid plexus or the middle cerebral artery, or a distant effect on the cavernous sinus or Gasserian ganglion.

II.—By Altering the Intracranial Pressure.

(1) The effect of raising the intraventricular pressure has been noted in four cases. Warm Ringer's solution was quickly injected into the ventricles in the course of ventriculography, before the removal of any cerebrospinal fluid. In two cases no headache occurred. In a third case this caused an exacerbation of occipital headache which was already present. It is interesting that in this patient, traction on the dura mater lining the posterior fossa, in the manner already described, did *not* give rise to any headache. Contralateral frontal headache resulted from a fourth similar experiment, in which the intraventricular pressure was suddenly increased. It should be noted that injecting fluid into the ventricles in these experiments raised the general intracranial pressure, as well as the intraventricular pressure. Consequently its effect may not necessarily have been due to distension of the ventricle. In fact, we have seen that direct pressure on the wall of the ventricle does not cause pain.

(2) In three cases of high spinal cord tumour, Ringer's solution was injected into the cisterna magna, before the injection of lipiodol for the purposes of radiological examination. In one case, after the injection of only a few cubic centimetres of fluid, the patient immediately complained of headache affecting the front half of the head. The headache rapidly subsided as the fluid was withdrawn. In the other two cases, the injection of 10 c.c. of fluid had no such effect.

(3) Before opening the dura mater in the course of a cerebellar exploration, I have observed that 20 c.c. of Ringer's fluid injected under the dura mater, probably into the subdural space, has resulted in homolateral occipital headache, which gradually disappears as the fluid escapes. It is usual in posterior fossa operations, to relieve the intracranial tension by

tapping an occipital horn, so that the dura mater may be opened with the least risk of damaging the brain, and the escape of ventricular fluid may be aided by gentle pressure upon the dura mater. This has on occasion been accompanied by occipital headache, although the fluid escapes freely through the needle. In one case when the gentle pressure on the cerebellar region was removed, the pain suddenly became *more acute* for a few seconds.

(4) Compression of the jugular veins for two minutes induced headache in six out of nine cases, and in four of these, the resting intracranial pressure was not above 200 mm.

(5) In many cases headache was produced by suddenly *reducing* the intracranial pressure. One of the patients in whom jugular compression produced headache, stated that the headache became much *worse* as the compression was removed. A subdural hæmatoma was subsequently found over the right hemisphere: it is noteworthy that the experimental headache was quite similar to his usual headache, being situated in the right side of the forehead.

(6) In five cases, when the lateral ventricle was tapped, the sudden escape of fluid was attended by considerable pain. On one occasion the intraventricular pressure was 550 mm., the patient being seated, and bifrontal headache occurred when the pressure fell below zero. On disconnecting the manometer, air hissed into the ventricles, and the headache completely subsided. In another patient with a frontal glioma, the pressure at ventriculography was 270 mm. When the ventricle was tapped on account of headache during the operation an hour or so later, the pressure was zero and the headache was relieved by pressing on the dura mater.

(7) The sudden release of fluid pent up in an arachnoid cistern has been noted twice to give rise to headache. When defining the lateral margin of a large suprasellar meningioma near the anterior clinoid process and the internal carotid artery, there was a sudden gush of cerebrospinal fluid from the cisterna chiasmaticus. As the fluid escaped, the patient complained of prolonged and severe aching in and over both eyes. In another case the puncture and sudden release of fluid from a much distended cisterna magna caused headache, so intense, that the patient was unable to state where it was.

(8) To illustrate the production of headache by decreasing the intracranial pressure, I will describe details of experiments upon a man who had an enormous cystic tumour of the anterior half of the right cerebral hemisphere. Many years previously a right subtemporal decompression had been performed with relief of his symptoms for a long period. A mano-

meter was connected to a needle in the cyst, and another to a needle in the opposite left ventricle. The initial pressure on each side was the same, 195 mm. After 25 c.c. of cerebrospinal fluid had escaped from the left ventricle, the pressure was 120 mm. each side, and headache gradually developed. With each further decrease in the pressure as fluid escaped from the ventricle, there was an exacerbation of the headache, but pressure upon the decompression gave complete relief. When the pressure fell as low as 10 to 40 mm. the headache, which was fairly severe all over the forehead and in the decompression, was made much worse by pressing on the decompression. At this stage, tilting the table so that the head was lowered increased the pain, and jugular compression and the intravenous injection of histamine also made the headache worse. The headache now remained fairly constant in intensity, and taking further fluid out of the ventricle or putting some back did not influence it. Although this headache was clearly induced by reducing the intracranial pressure, it could not be relieved by reconstituting the normal pressure, but subsided spontaneously in a few hours. This suggests that a change occurred in the sensitive tissue concerned, which was not immediately reversible.

III.—Combined Ventriculography and Encephalography.

It has always appeared to me as a significant fact that the procedure of ventriculography is usually associated with little or no discomfort, yet encephalography is intensely painful. When air is injected into the lumbar theca in the sitting position, headache usually commences after the replacement of about 20 c.c. of fluid, and is felt first in the occipital region, spreading subsequently to the vertex and forehead. Jugular compression provides some relief from the pain, more especially in the earlier stages than later when most of the cerebrospinal fluid has been removed. The pain is bilateral, but if the air be injected with the patient in the lateral position, then headache develops only in that side of the head lying uppermost. On sitting up, the pain becomes much more severe and spreads to both sides of the head equally. Penfield (1927) has made similar observations, and has proved radiologically that the air passes to any desired part of the vault with the production of a headache on that side.

I shall now describe an experiment combining ventriculography and encephalography. The usual parietal burr holes were made, and with the patient seated, a needle was inserted into the lumbar theca; its stylet was not yet removed, so that fluid should not escape. The ventricles were tapped and the fluid contents replaced by air without any discomfort. With the needles still in position so that there was a free communication between the ventricles and the external air, lumbar insufflation of air was now performed. After some 20 c.c. of fluid had been replaced by air the usual headache developed. The experiment was repeated in another patient with precisely similar results.

Since headache does not occur in ventriculography when usually little or no air enters the subarachnoid spaces, and since headache *does* develop in encephalography with the ventricles kept at normal atmospheric pressure, one may conclude that in these circumstances the responsible sensitive structure is not within the ventricle. The sensitive mechanism must be related to the dura mater with its vessels and sinuses, or the pia-arachnoid membranes and enclosed vessels, provided one assumes that the brain tissue itself is insensitive.

From the study of clinical material it has already been demonstrated that the absolute value of the intracranial pressure bears no constant relation to the presence or absence of headache. On the other hand the experimental observations recorded in this section clearly indicate that the sudden increase or decrease of a pressure previously normal or abnormal readily causes headache. A rapid reduction of the pressure is perhaps the more conspicuously successful method. The conclusion may therefore be drawn that *it is the sudden variation in the intracranial pressure which induces experimental headache, not the steady pressure itself.*

IV.—Collapse of the Brain.

A most unusual and dramatic cause for pain was observed in five patients with colloid cysts of the 3rd ventricle or basal ganglia tumours, in each of whom ventriculography had demonstrated grossly dilated ventricles. The ventriculography was performed immediately before operation and as much fluid as could be obtained was replaced by air with insignificant discomfort. In order to expose the tumour a piece of brain was excised so that a wide opening was made into the ventricle. When the air which was gently distending the ventricle suddenly escaped, the whole hemisphere collapsed like a punctured balloon. This sudden collapse of the brain was associated in each case with an immediate intense pain in the head. The precise distribution of the headache was not determined, and it disappeared after a few minutes. The significance of these observations will be discussed later.

V.—Headache Produced by Histamine.

Pickering and Hess (1933-34) were the first to make a detailed study of the headache which results from the intravenous injection of histamine acid phosphate. Their valuable contribution has been entirely confirmed by many other workers. The intravenous injection of 0·1 mgm. of histamine in normal subjects usually produces a bifrontal throbbing headache which develops about forty-five to sixty seconds after the injection, and subsides in the course of five to ten minutes. Histamine is a vasodilator, and consequently within a few seconds of its injection the systemic blood-pressure falls, and the cerebral vasodilatation causes the cerebrospinal fluid pressure to rise, by reason of the increase in the volume of the brain and its cortical vessels. In their experiments Pickering and Hess found that the headache developed when these changes were subsiding; in particular when the cerebrospinal fluid pressure was falling, and the blood-pressure was rising to normal. Moreover they showed that the headache might be relieved either by raising the intracranial pressure, or by lowering the blood-pressure. Clearly, the headache produced in this manner cannot be due to a rise in the intracranial pressure.

In order to compare the headaches of intracranial tumour with that produced by histamine, I have injected histamine into fourteen patients suffering from tumour. In three no headache occurred, and in normal persons histamine does not invariably cause headache. In each of the remaining eleven patients, the headache which occurred was similar in quality and distribution to that produced by their tumour. If the headache due to the tumour presented peculiar features, such as restriction to one side, then the headache from histamine had the same characteristics. One case illustrates this most conspicuously. The spontaneous headache for which the patient sought admission to hospital was an intense pain over the right side of the forehead, spreading up to the vertex, and as the headache developed, so the whole side of the forehead broke out into profuse sweating. Histamine produced an identical headache and sweating.

It was not possible to check these studies by measuring the pressure of the cerebrospinal fluid, but the changes in the blood-pressure were recorded, and it was found that the headaches always began as the blood-pressure was returning to normal. Clearly, in subjects suffering from a tumour, as in normal subjects, the headache produced by histamine cannot be due to the rise in intracranial pressure.

I have endeavoured to determine whether histamine causes headache by virtue of its effect on the vessels of the dura mater, or on the cerebral vessels. The minor operation of cerebral arteriography performed under local anæsthesia has presented this opportunity, and in thirteen patients I have injected histamine into the carotid arteries. Three of the patients experienced no headache at all. In the remaining patients, histamine was injected fifteen times into the common carotid artery, and headache resulted every time at intervals of from three to sixty seconds after the injection (Chart 4). Six of the headaches were confined to the side of the injection, and the remaining nine were either bilateral or developed earlier on the homolateral side and affected it much more than the contralateral side. On six occasions the injections were made consecutively into the internal and external carotid arteries of the same side. On five occasions, injection into the internal carotid artery was followed by homolateral headache, which in one case very slowly became generalized. In these same patients, however, *no* headache at all was produced by injecting the histamine into the external carotid artery. The sixth case was unusual, for injection into the internal carotid artery did not cause headache, but a very faint generalized headache slowly developed thirty seconds after the external carotid was injected.

CHART 4.

THE EFFECTS OF INJECTING HISTAMINE INTO THE CAROTID ARTERIES.

- 15 injections into the common carotid artery :
    - in 6 cases, headache was entirely homolateral.
    - in 9 cases, headache was worse on homolateral sides, or equal each side.
- 6 injections into the internal carotid artery :
    - in 5 cases, headache was homolateral.
      (becoming slowly generalized in one case).
    - in 1 case, headache was absent.
- 6 injections into the external carotid artery :
    - in 5 cases, headache was entirely absent.
    - in 1 case, faint generalized headache occurred.

The middle meningeal vessels are divided during the course of many intracranial operations, either at the foramen spinosum, or at the junction of the floor and the lateral wall of the middle cranial fossa. Histamine was injected intravenously into several patients who had had such an operation, and headache was felt on both sides of the head.

Several conclusions may be drawn from these experiments. The rapidity with which some of the headaches developed and their restriction to the side of the injection suggest that this experimental headache depends primarily on an alteration in *calibre* of the intracranial blood-vessels. Furthermore, there is strong evidence that the vessels affected are the cerebral vessels, branches of the internal carotid artery, and not the meningeal vessels of the dura mater derived ultimately from the external carotid artery.

The Effects of Sympathectomy and of Trigeminal Nerve Root Section on Histamine Headache.

Pickering and Hess stated that the removal of the stellate sympathetic ganglion did not abolish histamine headache. I have confirmed this in four cases. They noted, however, that the headache did not develop on the side of operation in patients in whom the trigeminal nerve had been divided. I observed the effect of histamine injection in seven such cases in whom the sensory root of the trigeminal nerve had been completely divided. In three cases, my observations confirmed those of Pickering, for headache was restricted to the forehead and temple of the normal side. In one of these patients, the headache also affected the back of the head, equally on both sides. In two other cases, however, the headache was equally distributed over both sides of the head, one of the patients stating spontaneously that the pain was worse on the side of the operation. In the two remaining cases, the injection of histamine did not give rise to any headache. One of these subjects was willing to co-operate further, so I injected 10 c.c. of air into the lumbar theca while he was in the sitting position. Headache developed at first in both sides of the back of the head, and later affected the forehead and temple of the normal side only.

Observations on the Relief of Headache.

The relief of headache has been studied but with less successful results, for the provocation of a headache by experimental methods has been effected far more readily than its relief. Raising or lowering the head of the bed has occasionally given relief, but either position has been found helpful in cases of high intracranial pressure. If the headache was associated with an abnormally low pressure, elevating the foot of the bed usually abolished it. There has been no convincing evidence that amyl nitrate, histamine, or ergotamine tartrate had any consistent effect on the headache.

The intravenous injection of a hypertonic solution of sodium chloride or glucose has at times given considerable relief. The following two cases are good examples.

(1) A boy, aged 16, had experienced headaches and vomiting for three weeks before admission to hospital. The headaches were bifrontal and paroxysmal in type, associated with pain and stiffness of the neck. An operation was performed for the removal of a cerebellar angioma which had bled, causing acute hydrocephalus. Prior to the operation, the headache became so intense that he was given 40 c.c. of a 15 per cent. solution of sodium chloride. Relief was afforded almost immediately, and he said he felt better than at any time during the preceding few days.

(2) A woman, aged 30, had had paroxysms of agonising headache for three weeks before admission to a nursing home. Although drowsy, the recurring headaches were so severe that she had not slept for four successive nights. Following the intravenous injection of 80 c.c. of a 50 per cent. solution of glucose, the headache was greatly relieved, and the patient was able to sleep. At operation next day a colloid cyst of the third ventricle was removed.

A moderately severe headache was immediately relieved by tapping the ventricles, the tension being considerably above normal. Three times, partial relief was occasioned by tapping a cystic tumour. One of these was a recurrent cystic glioma of the frontal lobe, and the pressure of the cystic fluid was only 70 mm. The headache was somewhat relieved as fluid dripped from the needle, but if vigorous aspiration were attempted, the headache immediately became worse.

I am indebted to Professor Paterson Ross for the opportunity of studying a patient who had had a successful subtemporal decompression many years ago for symptoms of a cerebral tumour. He sought readmission to hospital on account of symptoms suggestive of a recurrence of the tumour. As part of the investigation which subsequently excluded the likelihood of a tumour, a lumbar puncture was performed. A day or so later, every time the patient sat or stood up, the decompression became deeply concave, and he experienced intense contralateral frontal headache. The headache subsided when he lay down, and the decompression became less concave. This condition persisted several days, until 50 c.c. of warm saline were slowly injected into the lumbar theca when the patient was in the lateral position. The decompression now bulged and when he sat up, the headache no longer occurred. He remained practically free from headache without any further injections of fluid.

Discussion.

The observations presented in this paper, and those published by others, afford incontrovertible evidence that certain areas of the dura mater possess considerable sensitiveness when suitably stimulated, and it has been almost universally accepted that the dura mater and its vessels are the sensitive structures responsible for the production of headache. From the clinical observations recorded in this paper it is clear that an explanation which is based upon dural sensibility is inadequate. Many speculations have been advanced to explain precisely how the dura responds, and I will indicate further difficulties which prevent an acceptance of them.

Dural sensibility as tested at operation depends upon a fairly severe pressure, which if prolonged, would probably result in tissue ischæmia. The pain which results is usually fairly sharp and confined to a small area, the position of which the patient can locate with fair accuracy, but the difficulty in finding a suitable description for spontaneous headaches is common experience, and their location is usually vague. An example of this is offered in cases of tumour of the cerebellum adherent to the tentorium. Pain is rarely felt in the eyes, though this is the characteristic result of stimulating the tentorium. Moreover, dural pain ceases shortly after the stimulus is removed, but altering the intracranial pressure causes headache which frequently persists for several hours, in spite of the restitution of the normal pressure. The suggestion has already been made that this signifies some change in the sensitive tissue which is only slowly reversible, and cannot be a simple pressure effect upon the dura mater.

How can a tumour so stimulate the dura mater as to produce frequently recurring paroxysms of headache, the intervening periods being free from pain? If it is merely an increase of intracranial pressure which stimulates the dura mater, why does not headache regularly occur in normal people when jugular compression is performed, or each time one coughs violently? There are many who will maintain that this fails to excite headache because it increases the pressure uniformly within the skull. They consider the stimulus to arise from unequal pressures on the sides of the tentorium or falx. But every morning on rising the brain must weigh more heavily on the tentorium, with no ill-effects. One may press on a subtemporal or cerebellar decompression almost to the point of damaging the brain, yet apart from slight discomfort the patient denies any real headache. If the dura mater were the responsible structure, one would expect the pain to be more frequently referred to areas supplied by the Gasserian ganglion. Such associated pains in the face do occasionally occur, as distinct from so-called false localizing signs due to direct pressure upon the ganglion. They are met with more frequently amongst patients with a pituitary tumour, and I believe, in those cases in which a tumour gains a secondary attachment to the dura mater, such as occurs with a cerebral abscess. That headache occurs in cases of pituitary tumour is considered to be strong evidence that pressure on the dura mater causes headaches, by reason of the confined dural limits in which this tumour grows. It seems very probable that more than one mechanism may be operating in these cases. The poorly-localized, dull bifrontal headaches may be caused in the same manner as in other intracranial tumours, whereas the radiating neuralgic facial pains may well be referred from the dura mater.

The headache due to histamine cannot be explained by dural stimulation. It occurs only with a falling intracranial pressure, and is relieved either by increasing or by lowering the blood-pressure, and I have already shown that the middle meningeal vessels are not responsible.

This question of the dural origin of headache must now be finally answered, before passing to the constructive portion of the discussion. It is conceded that direct stimulation of the dura mater by direct pressure, or by its involvement in the disease, may occasionally be the cause of headaches. Such headaches are of a special neuralgic type; they usually occur in cases of pituitary tumour and only rarely in cases of tumour elsewhere in the cranium. But from the available clinical experimental evidence the conclusion is inescapable that the dura mater is not the sensitive structure which is responsible for the common headaches of intracranial tumour.

* * * *

The only intracranial tissue other than the dura mater which is sensitive to suitable stimuli is apparently the cerebral blood-vessels. That headache might be vascular in origin has already been suggested, and this aspect of the subject will now be discussed. I shall proceed to indicate in what way the vascular changes which occur during histamine headache may be related to the statement that "it is the sudden variation in intracranial pressure which induces experimental headache." A proposition in explanation of headache will follow further elaboration of the argument.

Let us consider the forces within the cranium which may influence the calibre of the smaller cerebral arteries. There are three variants: the intravascular pressure of blood distending the vessel wall, the tone of the vascular musculature, and the intracranial pressure which supports the outer surface of the vessel—this may be termed the extravascular pressure. Since these forces act within a semi-rigid container, the variation of one beyond certain limits must influence the others to some degree. Histamine injected intravenously causes generalized vasodilatation; the blood-pressure, and therefore the cerebral intravascular pressure falls, and because of the increase in calibre of the cerebral arteries the intracranial (extravascular) pressure passively rises. As the effect of the drug subsides, the tone of the systemic arteries recovers more rapidly than that of the cerebral arteries, so that the tone of the cerebral vessels is still less than normal when the intravascular pressure has regained its former value. It is at this point that headache is appreciated. Clearly, as Pickering and Hess pointed out, during this period of lag in the return of vascular tone, the walls of the cerebral vessels are being subjected to an unusual degree of tension, and they suggested that it was this abnormal state of tension which gave rise to the headache. The relief obtained by increasing the intracranial pressure and consequently giving greater support to the vessel walls, and the relief which resulted from diminishing the blood-pressure and the distending effect of the intravascular pressure, is evidence which strongly supported this view. When histamine was injected intravenously into a patient with a recurrent right frontal glioma, in whom an enormous cerebral hernia had developed through a wide bone defect, the headache was more severe on the right side of the head. This may be explained by the lack of external support to the vessels of the right frontal lobe which the intact skull would have afforded.

Clark, Hough, and Wolff (1935) have performed experiments which still further favour this explanation of an abnormal state of tension in the walls of the cerebral blood-vessels. Simultaneous photographic records were made of the pulsations of the temporal artery, and of the cerebral vessels as reflected in the pulsations of the cerebrospinal fluid. The increase in the excursion of each pulsation was very much greater in the cerebral vessels than in the temporal artery, during the period when histamine headache was experienced.

Since the intravascular pressure is opposed by the extravascular pressure and by the tone of the vessel wall, any sudden drop in the extravascular pressure—as occurs when the ventricle is tapped—would cause a relative degree of abnormal stretching of the vessel wall, unless the tone of the muscle were immediately adjusted. Such an experimental procedure was found to be very successful in provoking headache, and that it may be due to a change in vascular tension is an hypothesis comparable with that given for histamine headache. Whether it is the adventitia or the media, or both, which respond to the stimulus is not clear.

Can the headaches due to an intracranial tumour, or due to an experimental rise in the intracranial pressure, be explained upon a similar basis? In order to answer this question, the behaviour of the cerebral circulation in the presence of an intracranial tumour must be briefly considered.

In order to maintain an adequate blood supply to the brain, a delicate balance is maintained between the lumen of the smaller cerebral arteries and the velocity of the blood flow. The velocity of the flow of blood through the cerebral vessels depends upon the relation between the intracranial venous pressure and the intracranial arterial pressure. According to Wolff and Blumgart (1929) when the intracranial pressure is raised a slowing of the blood-flow occurs. In consequence of this, cerebral veins, capillaries, and arteries dilate in order that the blood supply may be adequately maintained. The slowly growing tumour gradually compresses the brain in order to acquire room and in so doing imperils the blood supply; this necessitates some degree of vasodilatation and consequently there is an increase of pressure within the capillaries. It is this progressive vasodilatation which results in the rise in intracranial pressure in the course of the disease. When the cerebrospinal fluid pressure is measured, one obtains an index of the cerebral capillary pressure, and the venous pressure is closely related. An increase of intracranial pressure in disease indicates primarily an increase of the pressure within the arterioles and capillaries. It is no measure of the bulk of the tumour, for at post-mortem the pressure is zero. This is in accord with clinical experience, for the intracranial pressure may be normal in a patient with a very large meningioma, or in one with a condition such as a colloid cyst of the third ventricle which has nevertheless produced conspicuous dilatation of the ventricles. So slow is the growth of the tumour that the brain adapts itself by gradual displacement, compression, and even atrophy. The process is too slow to affect the general intracranial circulation until the terminal stages when the limits of compensation have been reached, and although it is quite evident that the disease has been present for a long time, only a relatively short history of recent headache may be obtained. On the other hand, a more rapidly growing tumour such as a glioma, although it may be small, will readily cause progressive disturbance in the cerebral circulation, resulting in a raised intracranial pressure and liability to headaches. In order to maintain an adequate blood flow fluctuations must occur in the tone of the vessel walls, and consequently in the intravascular and extravascular pressures. In this relatively labile state, conditions are highly favourable to the disturbance of proper balance between these three variants. Such a lack of balance will subject the vessel wall to an abnormal strain. The view is therefore advanced that *the headache in intracranial tumour is due to some disturbance of the tension of the walls of the cerebral vessels.* It is this disturbance of tension which provides the adequate stimulus for the excitation of pain.

Many clinical observations give direct support to this explanation of headache. Attention has already been drawn to the similarity between the headache produced by histamine and that due to a tumour. This similarity is remarkable since histamine evokes the peculiarities of certain tumour headaches, and indicates that one and the same sensory structure is being stimulated. The pain which occurs during operations when the brain collapses may be deemed vascular in origin, being due to the sudden gross distortion of the arterial tree. An alternative explanation might be offered in these cases, and for the headache of encephalography. Considerable traction must be exerted upon the veins entering the great sinuses as the brain falls away from the dura mater, and this traction may stimulate the sinuses. This however implies a dural origin for the headaches and such can no longer be admitted. Moreover, the pain of collapse of the brain was momentary although the tension upon the veins was maintained. The headache of encephalography endures for some hours and is but slightly relieved in the recumbent position, in which position most of the veins will be relaxed. The unilateral headache which follows the intrathecal injection of a small quantity of air when the patient is lying in the lateral position may be due to a local difference in the support afforded the cortical vessels.

The clinical evidence that in the majority of cases the tumour is situated on the same side as the unilateral headache, suggests that the headache depends upon some local feature, and some abnormality of vessel tension forms an adequate basis for explanation. The walls of vessels in the immediate vicinity of a tumour may well be in a different state of tension from those more distantly placed. Such strain may be dictated by some local vasomotor influence. A similar state was produced experimentally when histamine was injected into the carotid artery and caused homolateral headache. Paroxysmal headaches can also be satisfactorily explained in this way ; the variation of intensity in the headache may originate in some vascular crisis which has arisen in order to maintain an adequate blood flow. These crises will naturally become more severe during the closing phases of the illness, corresponding with the progressive intensity of the headaches. The frequent termination of these headaches in unconsciousness and in an epileptiform convulsion makes such an explanation reasonable.

Headache is frequently of minimal degree in elderly patients suffering from spongioblastoma multiforme. Not only may it be entirely absent, but the intracranial pressure is often normal, although at autopsy the tumour proves to be of considerable magnitude. This type of glioma is very malignant, and in spite of its rapid increase in size, the surrounding brain becomes extensively infiltrated rather than compressed. In this way the joint bulk of the tumour and the brain may not be much increased, and the cerebral circulation is not hampered. In a personal communication, Dr. J. G. Greenfield suggests an alternative explanation. In elderly persons the subarachnoid spaces are frequently very capacious and consequently accommodation is provided for a considerable growth of a tumour without an undue rise in the intracranial pressure.

Gibbs (1934) analysed the frequency of the various symptoms produced by tumours in different parts of the brain. He found that the curve of the incidence of severe headaches followed that of the incidence of generalized convulsions more closely than the curve of any other symptom. This observation is of interest when considered with the cases previously quoted, which demonstrated the similarity between the headaches due to a tumour and those due to an epileptiform seizure. The latter headaches may very likely have a vascular origin, for there is general agreement that during convulsions widespread changes occur in the diameter of the pial arteries, although the significance of these changes is not yet appreciated. Penfield (1933-34) states that the typical vasomotor phenomena consist of an arrest of visible pulsation in the arteries during the seizure, followed by a period when the vessels pulsate more violently and more rapidly, and the veins may assume the hue of arteries. Except for the cessation of pulsation, this description accurately resembles the appearance of the exposed brain after the patient has received an intravenous injection of histamine during the course of an intracranial operation. Furthermore, it is during this period of excessive pulsation that histamine headache is appreciated. It may be asked why many epileptics do not experience headache. The explanation probably lies in the degree of the vascular distortion. In their experiments, to which reference has already been made, Clark, Hough and Wolff concluded that the "threshold" for headache varied widely in different subjects. Of paramount importance was their observation that "*in a given individual after a vasodilator agent (histamine) which caused headache, the distortion of the vessels was nearly twice that following another vasodilating agent (carbon dioxide) which caused none.*"

There are several serious objections to this suggestion of a vascular origin of headache which must be answered. The most obvious and the most difficult to refute is based on anatomy. Along what pathways are the afferent stimuli conducted, and what course do the nerve fibres take in order to reach the brain? It is known that no afferent fibres descend from the superior cervical sympathetic ganglion, nor does stellate ganglionectomy prevent headaches. Furthermore it has been shown that total section of the sensory root of the trigeminal nerve abolishes headache, though not invariably. This evidence has hitherto only been interpreted as indicating that the meningeal vessels are the structures responsible for headache, and these have already been excluded. But it may be asked whether any branches pass from the Gasserian ganglion or from its sensory root, to join the carotid plexus and perhaps serve as an afferent pathway from the cerebral vessels. There is no evidence on this very important detail of anatomy. Stöhr (1928) only considers it, without committing himself; Dowgjallo (1929) states that branches pass from the trigeminal nerve to the carotid plexus, but gives no supporting evidence. In a personal communication, Professor Donal Sheehan informs me that he has made careful dissections of eight specimens of the cavernous sinus. In every specimen, he has found several connections between the Gasserian ganglion and the sympathetic plexus around the carotid artery. He points out, however, that from dissections alone, he is not prepared to say whether these connections convey sympathetic fibres to the 5th cranial nerve, or sensory fibres from the carotid artery.

There are some suggestive experiments which help to fill this hiatus in anatomy. Davies and Pollock (1932) found that reactions of pain were produced in animals when a stimulus was applied to the superior cervical ganglion, after all its branches had been severed except those fibres ascending into the skull on the internal carotid artery. These reactions were abolished when the trigeminal nerve and the upper posterior cervical roots on the same side were divided. They concluded that the pain was produced by some effect of the stimulus upon the structures innervated by the sympathetic nerves. This stimulus may well have set up an abnormal state of tension in the cerebral vessels, the afferent path for the pain being along the divided trigeminal and cervical nerves. This raises the question whether the vertebral arteries may not receive branches from the cervical nerves, in order to account for the occipital distribution of some headaches. Temple Fay (1931) has found that stimulation of the vertebral and basilar arteries causes pain in the back of the head and in the neck.

Similar conclusions may be drawn from the work of Penfield and Chorobski (1932), who have demonstrated that in monkeys, the vasodilator fibres to the cerebral vessels leave the brain by way of the facial nerve and gain the great vessels through the greater superficial petrosal nerve. Some of their experiments in nerve degeneration indicate that afferent fibres from the carotid plexus may join the geniculate ganglion and reach the brain through the nervus intermedius. They found that stimulating the distal end of the cut greater superficial petrosal nerve not only resulted in vasodilatation, but caused the animal to struggle when anæsthesia was light. This struggling was abolished when the trigeminal nerve was divided.

Levine and Wolff (1932) using galvanic skin responses as a criterion of pain, have made experiments on animals concerning the effects of stimulating electrically the blood-vessels and pia mater in various parts of the brain. They obtained results which indicated that afferent impulses were set up most frequently and of greatest magnitude when the larger arteries were stimulated. In addition to my own clinical observations, other surgeons have reported cases in which pain resulted from stimulating the largest of the cerebral vessels, such as the middle cerebral artery. As these observers remark, negative results in man may only signify that the adequate stimulus was not being employed.

Objections may be raised against evidence which is based on a comparison of headache due to intracranial tumour with histamine headache. It has been noted that histamine headache is relieved by lowering the blood-pressure by the use of a vasodilator. Such treatment for the headache of intracranial tumour usually gives no clear-cut relief. The headaches associated with an abnormally low intracranial pressure are, however, relieved by artificially raising the pressure ; this action may well be similar to the relief which jugular compression affords histamine headache. It is not suggested, moreover, that headaches due to tumour are due to vaso-dilatation, but that an abnormal state of tension of the walls of vessels acts as the adequate stimulus. Drugs which are believed to act upon the cerebral vessels are unsuccessful when employed to relieve the headaches of tumour. In this connection, the considerable relief afforded by the intravenous injection of hypertonic solutions is of great significance. Although this procedure is known to reduce excessive intracranial pressure, it should not be assumed that the relief of the headache is necessarily a direct result of this reduction of pressure. Wolff and Forbes (1928) observed through skull windows the effect on the cortical circulation of the intravenous injection of hypertonic solutions. Following a transient vaso-dilatation (which could be prevented by injecting the solution very slowly) the pial arteries and veins gradually decreased in calibre, and this vasoconstriction was associated with a fall in the pressure of the cerebrospinal fluid and a rise in the systemic blood-pressure. The work of others is quoted, in which increase in the tone and in the peristalsis of the bowel, and pallor of the bowel wall and of the spleen due to vasoconstriction, were also observed following the intravenous injections of hypertonic solutions. These authors conclude that there is probably a direct action of these solutions on plain muscle. It is clear that these experiments offer considerable ground for the belief that the relief of headache by such methods is due to an immediate and direct effect upon the cerebral arteries, and consequently give further support to the proposition. Such an explanation fully accounts for the striking rapidity with which relief follows the injection, for this frequently occurs before the procedure terminates, or a few minutes later. Clearly, this is too soon for the effect to be due to the gradual fall in the intracranial pressure which is effected by osmosis, though doubtless this delayed action prolongs the period of relief.

* * * *

I would like finally to put the headache of intracranial tumour into the perspective in which I view it in common with the disorders of the other great systems of the body. Abdominal pains may be considered to be either of somatic or of visceral origin, and Morley (1931) has emphasized the essential differences in character between these varieties of pain. Somatic pain has usually a sharp and stabbing quality, is often continuous and is accurately localized. Visceral pain on the other hand, has a distinctive dull quality which is difficult of description. It is often intermittent or spasmodic, and in sharp contrast to somatic pain it is imperfectly localized. Such descriptions can be most aptly applied to the headaches under discussion, of which there are two varieties. Those infrequent headaches in which a neuralgic element is prominent, and which were conceded to be possibly of dural origin, may be regarded as somatic pain. The common headache due to an intracranial tumour, to an epileptiform convulsion, or to an intracranial aneurysm, satisfies remarkably fully the criteria of visceral pain.

Visceral pain is the manifestation in consciousness of a protective mechanism. In the presence of any obstruction of its lumen, the intestine undergoes violent muscular contractions in order to rid itself of the obstruction. Although the intestine is insensitive to ordinary physical stimuli, it is now fully accepted that visceral pain arises only as a result of the adequate stimulus—an abnormal state of tension of the muscular walls. In the respiratory system, pain is almost entirely of somatic origin ; the visceral element has remained undeveloped, for the protective mechanism consists of a cough reflex. In certain diseases of the heart, the cardiovascular system is guarded against the dangerous strain of effort by a mechanism which produces anginal pain. Using this simile, the integrity of the central nervous system depends entirely upon an adequate supply of blood. In the presence of a tumour, this supply of blood is in danger. Headache may be regarded as visceral pain, indicating the perilous position of the brain, and a state of abnormal tension set up in the walls of its blood-vessels may be the adequate stimulus of visceral afferent fibres, the pathway of which is not yet clearly defined.

SUMMARY.

(1) This paper presents a study of the headaches provoked by intracranial tumours, with especial reference to the mechanism of their causation.

(2) The significance of the clinical varieties of these headaches is considered.

(3) Experiments are described which were performed in order to determine the sensitiveness or otherwise of the intracranial contents, and to elucidate the factors which provoke or relieve headache.

(4) The results of these studies are discussed in the light of the anatomy and physiology of the intracranial circulation, and of the physiology of the intracranial pressure.

(5) It is concluded that the dura mater is not the sensitive structure which is responsible for the characteristic headaches of intracranial tumour.

(6) It is suggested that the headache is caused by an abnormal state of tension in the walls of the cerebral blood-vessels.

It is a pleasure to offer my grateful acknowledgment to Professor Hugh Cairns, for suggesting the subject as worthy of research, for the facilities which are always available in his department to those interested in research, and for the stimulus of many fruitful discussions.

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"APHASIA" IN A PARTIAL DEAF-MUTE.

BY MACDONALD CRITCHLEY.

In an article contributed to the first volume of this Journal, Hughlings Jackson (1878) wrote: "No doubt, by disease of some part of the brain, the deaf-mute might lose his natural system of signs which are of some speech value to him." The case here recorded, sixty years later, furnishes strong support to Jackson's contention, although complete proof is still wanting.

Preoccupation with verbalization as the most obvious modality of language has diverted attention away from the non-verbal processes of speech. Obviously, spoken words are only one of several modes of "symbolic formulation and expression," and articulate speech is not essential in making known one's ideas or feelings. A tourist in a foreign country where the language is unfamiliar can contrive to make himself fairly well understood by calling upon the resources of gesticulation, just as he will manage to comprehend his entourage by studying their facial expressions and gestures.

At the outset it is necessary to be precise in our terminology. As Jackson taught, the word "pantomime," which should be restricted to that variety of dumbshow which aims at expressing an idea, should be distinguished from "gesture" which connotes those movements, especially of the hands and face, accompanying speech for the purpose of emphasis. Pantomime is silent acting while gesture is merely a kind of italicized speech. The relationship of pantomime to gesture is that of "propositionizing" to emotional utterance. It must be remembered that no sharp frontier divides gesture from pantomime—any more than emotional from propositional speech—and in some cases expressive movements can be assigned to either category.

The term "physiognomy" serves to denote the play of facial emotional movements, most of which are automatic rather than deliberate, and many of which are beyond the control of volition. This term also comprises the involuntary changes determined by emotional factors, mediated chiefly by way of the autonomic nervous system. Such phenomena as blushing, pallor, shivering, sweating, horripilation belong here.

Clearly, even articulate speech is at times nothing but gesture rendered audible. This view is borne out by the occurrence, in analogous form in all languages, of certain onomatopœic words, where the meaning is adequately conveyed by the sounds themselves. Some philologists and phoneticists have gone much further in attempting to trace a far closer alliance between gesture and vocal speech. Paget, for example, regards speech as an elaboration of phonated buccal-labio-lingual gestures. He finds an intimate connection between the phonetics of a word and its meaning. The suggestion is that man originally expressed himself by gesture, and "as he gesticulated with his hands, his tongue, lips and jaw muscles followed suit in a ridiculous fashion, understudying the action of the hands. Later, movements of the jaws and mouth actually supplanted the manual gestures, when it was found the expiration of air through the oral cavities produced a wide range of audible mouth-gestures or voiced-speech."

Expressive Movements in Aphasic Patients.

In cases of aphasia due to focal cerebral lesions, the role of gesture and pantomime forms an interesting though neglected subject. It may be said in broad terms that articulate speech is usually affected far more severely than expressive movement. When the aphasic defect is slight the patient can usually communicate by signs in unmistakable manner, even though the right upper limb is powerless. The pantomime falls short of normal standards however in respect of precision and range; this defect is as a rule directly proportional to the degree of aphasia. In some instances of total speechlessness with dementia, almost all power of expressing ideas and even feelings is lost; to this inability to communicate by signs and by words, the term "asemasia" was proposed by Hamilton. Hughlings Jackson (loc. cit.) recognized three grades of disordered function: (1) defect of speech; (2) loss of speech, where the patient is practically inarticulate and where pantomime is impaired; and (3) loss of language, where pantomime as well as speech is completely lost.

Nevertheless, aphasic patients may occasionally betray exaggerated expressive movements of all types. This feature may be noted at times in patients with jargonaphasia. Recent conceptions, which follow Goldstein, van Woerkom and others in studying disturbances of the "total behaviour" in aphasic patients, confirm this. According to Goldstein (1936), patients with amnesic aphasia are persons acting in the world rather than thinking or speaking about the world, and in such, expressive movements may be excessive.

Deaf-mutes.

There is one set of circumstances in which gesture language entirely ousts verbalization from speech. In a deaf-mute articulate speech is minimal, and an elaboration of pantomime becomes all-important. Here, a complex system of dactylology, with or without lip-reading, forms the usual channel for the interchange of ideas.

The question arises as to whether or not there exists an anatomical substratum comparable with the normal "zone of language" in the left hemisphere, and vulnerable to the usual morbid assaults. In other words, whether focal cerebral lesions can damage or destroy the execution of sign-language by a deaf-mute as Jackson originally hinted.

The following case-record demonstrates that a left-sided cerebral lesion can interfere with the performance of finger-spelling in a "partial" (i.e. acquired) deaf-mute:—

W. H. H., a man aged 42 years, first attended my out-patient clinic at the National Hospital, Queen Square, in 1930, on account of the effects of a stroke sustained six weeks before.

The patient was well until the age of 7 years when he gradually lost his hearing. As his disability steadily increased, he was taught finger-spelling. By the age of 14 years, being now stone-deaf, he was admitted to an institution for deaf-mutes. Here he remained three years; finger-speech was discouraged and he was taught lip-reading. After leaving the school he relied chiefly upon manual signs and finger-speech to communicate with others.

His stroke, which occurred on September 1, 1930, caused a right-sided paralysis, and for three days he was deprived of what little articulate speech had previously been possible to him. The paralysis improved considerably in the course of the next four weeks, and his speech also returned to some degree.

As soon as he was able to hold a pen, it was found that he could neither write nor perform on paper simple arithmetical calculations. It was also discovered that he could no longer lip-read. For the first few days after the stroke he was quite unable to understand people who communicated with him in finger-spelling. This ability returned in a few days, but he was still unable to reply upon his hands. His articulate speech was infrequent, and considerably altered; it was much too loud in tone, and he seemed "unable to regulate" his voice, so that when he wanted to emphasize a word, he merely raised his voice to a shout. The speech was furthermore dysarthric and ungrammatical; he seemed to rely very little indeed upon this means of communication.

He remained under observation for the next two years, during which time his condition changed little, if at all.

Repeated physical examination revealed a right-sided hemihypæsthesia, but no hemianopia; no loss of power in the arm or leg but a slight right-sided weakness of the face and tongue. The tendon-jerks were equal on the two sides and both plantar responses were flexor in type. No evidence of apraxia.

Investigations of the patient's aphasia were carried out through the intermediary of the late Rev. Mr. Bradbury, chaplain to the deaf and dumb institution, who acted as interpreter.

Some ability to lip-read was beginning to appear, but the defect was still very considerable. The power to understand others talking upon their hands had returned.

A large number of defects were present, however, in the patient's own efforts at finger-spelling. According to the interpreter the chief faults comprised:—

(1) Confusion of the vowels, viz. he might point to "A" instead of "E."

(2) His finger-speech no longer formed sentences but was short, "telegrammatic" and ungrammatical.

(3) If asked to indicate the five vowels he started correctly but was unable to finish. When asked to go through the alphabet he was at times unable to complete the task.

(4) The movements of the hands were manifestly erratic and jerky; "there is no smoothness about them." Possibly they were executed more slowly than usual, but the patient and the interpreter were not in agreement upon this point. According to the former . . . "my deaf friends say I go too quickly and that if I were to go more slowly I would get along better."

(5) Words were omitted, and wrong words were used.

Tests with writing, recognition of colours, clock-reading, word-building with cards, typing, and reading were executed pretty well on the whole. Calculations were carried out with some difficulty.

Here then is a partial deaf-mute who as the result of a left-sided cerebral lesion, presumably small and circumscribed in area, developed an "aphasia" as regards his dominant method of symbolic expression. Such a case recalls the idea at one time held by Liepmann that motor aphasia is a mere variant of motor apraxia ("apraxia of the lips and tongue") and this particular case might perhaps be regarded by some as an instance of "dactylological apraxia." The specialized use of the hands as organs of speech in the case of deaf-mutes, lends support to Liepmann's view.

The literature holds no record of any other such case. Closest in approximation is the description by Grasset (1896) of another deaf-mute who lost his ability to make hand-signs after a cerebral vascular lesion. The patient, an arteriopathic deaf-mute of 50 years, rather gradually developed signs of a cerebral softening. There was some lowering of the general intellectual level, so that he had ceased to be able to manage his business, and his memory and rate of comprehension had deteriorated. Nevertheless, he was able to read with understanding, and also to comprehend finger-talk in others. He was, however, unable to reply with the right-hand finger-alphabet but could do so promptly with the left hand. If asked to spell out the alphabet he started by indicating with difficulty the letter "A," then with more difficulty the "B," and then failed to sign the remaining letters. Using the left hand he could demonstrate the alphabet rapidly and correctly. If shown printed words and told to spell them on his fingers, he succeeded with his left hand but failed with his right. At the same time there was a difficulty in writing. The right arm showed some defect of motor power and of co-ordination, though insufficient in degree to account for the failure to write or to finger-spell.

In this patient, however, the finger-spelling had always been carried out with the right hand only—as is the rule with deaf-mutes in France and the U.S.A. After the stroke, the patient was able to perform finger-spelling correctly with the left hand, though scarcely at all with the right. Such an inconsistency plainly reveals a different kind of speech affection than was present in my case, and is best recognized as an example of apraxia, or possibly of finger-agnosia (Gerstmann's syndrome). An integrity of all the preverbal processes which may loosely be described as "internal speech" seems to have been present in Grasset's case, but not in the case here recorded.

Grasset concluded that in the deaf-mute, a centre for manual speech develops in the cortex, independent of the motor area of the upper limb. He tentatively located this in the foot of the second frontal convolution of the left hemisphere.

In discussing the language of deaf-mutes it is necessary to draw attention to a very important though little known fact. Congenital deaf-mutes universally employ in addition to their complicated uni- or bimanual dactylology or finger-spelling, a kind of "natural sign-language." This is a sort of pantomimic shorthand, whereby a movement serves to indicate an entire word, a phrase, or even a sentence. The "natural" sign-language is not necessarily taught in schools (indeed its use may actually be discouraged). It is not committed to textbooks, and there are only a very few and rather inaccessible pamphlets on the subject. It is mainly "picked-up" by deaf-mutes in their institutions and passed on from one to another as a sort of tradition.

A number of interesting features are traceable in this sign language. In addition to its inherent advantages of rapid execution it possesses yet another outstanding merit. The natural sign-language is largely "international" and surmounts racial and linguistic barriers. Deaf-mutes of all nationalities have little difficulty in understanding and communicating with each other.

This universal comprehensibility follows because most of the gestures are obvious in their meaning, and represent a symbolism which is universally accepted and employed. These symbols belong to the category of "natural" signs, either because they mimic the specific appearance or function of the object concerned or because they are so traditional and ingrained as to be obvious to peoples of every race and age. In addition to these "natural" or "instinctive" gestures, there are a smaller number of "cryptogenetic" symbols where the meaning and origin are not selfevident. Such gestures may vary from country to country, and even from one institution to another. Actually even these signs are not altogether empirical, but the various processes in their development have become distorted or eliminated, so that the end-result is no longer recognizable at sight.

There are still other circumstances where gesture language usurps—either habitually or on occasion—the place of articulate speech. In some primitive societies, gesture may constitute a *lingua franca* between peoples speaking divers languages which are unfamiliar. Such sign-languages exist amongst the Queensland aborigines (Howitt (1891), Roth (1897), Stirling; and among the North American Indians (Seton (1918), Tomkins (1926)). These have been adequately studied and documented. So similar are they to each other, and also to the natural sign-language of deaf-mutes, that they are mutually comprehensible. Many of the signs are identical and others so little different as to cause no doubt as to their meaning. These are striking observations which have been confirmed by various writers on many occasions.

It is not yet known whether a far-reaching likeness exists between these systems and the various other elaborate sign-languages which are practised. Although studies have been made of the gestures employed in the Hung Secret Societies of China (Ward); the Neapolitan slums (de Jorio); the Trappist and other monastic orders (Herrgot; Aungier), no work of a comparative character has been attempted. A superficial study suggests that there is but little similarity between these systems and the "natural" sign-languages of the deaf-mutes and the aborigines. The factors of ritual and of secrecy no doubt go far to obscure the meaning of the other sign-languages and introduce an element of artificiality.

In the case of the deaf-mute patient described in this paper, the "natural" sign-language was not impaired. The circumstances were unusual, however, in that he had never been proficient in this means of communication and preferred lip-reading or finger-spelling. This may be ascribed to a variety of reasons, and especially to the fact that hearing was intact for the first few years of life, during which period articulate speech developed normally. For this reason the patient cannot be regarded as an example of "complete" or congenital deaf-mutism. Hughlings Jackson's surmise therefore remains unverified inasmuch as it explicitly referred to a natural system of signs and not to finger-spelling. It is justifiable to suggest that a much more severe lesion would be required to abolish the more primitive sign-language than the elaborate system of dactylology.

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GLIOMATOSIS CEREBRI.[1]

BY SAMUEL NEVIN.

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INTRODUCTION.

FROM time to time occasional reports of cases, characterized pathologically by a diffuse cellular overgrowth throughout the wide areas of the cerebral hemispheres, have appeared in the literature. These have generally been regarded as diffuse tumours, but they have varied considerably as regards the actual type of the cell constituting the overgrowth and they have been described by the different authors under different titles.

In 1910 Landau, under the title "Diffuse Glioma of the Brain," described the case of a male, aged 29, who died suddenly after a three years' history of intermittent headaches and epileptic attacks. The patient showed no physical signs apart from an intention tremor of the left arm and leg, and a slight ptosis of the left eye. At autopsy there was found a diffuse enlargement of the anterior part of the right cerebral hemisphere, which showed on section softening and œdema of the white matter, with slight loss of colour and some increase in thickness of the grey matter. Microscopical examination revealed a widespread but very variable gliomatous degeneration of the cortex and the thalamus on the left side. The cells which were regarded by the author as undifferentiated glial cells, were superimposed upon the normal tissues, with accumulations round the nerve cells and along the vessels. There was calcification of the blood-vessels and in the nerve cells. The author considered the condition as a diffuse glioma which had arisen at different points in a congenitally abnormal tissue, and had spread by continual involvement of other regions in the pathological process. Hildebrandt (1906), under the title of "Gliomatous Hypertrophy" of the right cerebral hemisphere, and Schwartz and Klatter (1927), under the title of "Diffuse systematic overgrowth of the glial apparatus of the brain," have recorded somewhat similar cases.

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[1] From the Hospital for Nervous Diseases, Maida Vale.

Cassirer and Lewy (1923) described the case of a woman aged 37, who, after a nine months' history of failure of vision and epileptic attacks, died following an operation for relief of increased intracranial pressure. At autopsy the right hemisphere was found to be swollen, and of slightly increased consistency. Sections showed large areas of demyelinization in the right cerebral hemisphere, which had arisen as the result of a mature glioma. This in its centre had produced mostly fibres, but in its periphery it was very cellular and grew in a fingerlike manner into the cortex and even through this into the pia. The author regarded the case as exemplifying a blastomatous type of diffuse sclerosis.

More recently Foerster (1934) has described, under the title "Central Diffuse Schwannosis" in Von Recklinghausen's disease, the case of a girl, aged 11, who within a period of six weeks developed severe headaches, loss of vision, and weakness of the left side. The patient had skin changes as in Von Recklinghausen's disease, namely numerous pigmented spots and small isolated fibromata on the trunk and limbs. Death occurred with symptoms of increased intracranial pressure. At autopsy there was found a great enlargement of the basal ganglia and thalamus on both sides. There was also diffuse swelling of the brain stem. Microscopical examination showed a dense cellular overgrowth in these regions composed of elongated, cigarette-like nuclei, which were arranged parallel to one another along the nerve fibre bundles. These cells were also found over wide areas of the cortex, but less densely placed except underneath the pia and along the blood-vessels. Santha (1935-36) has described a similar case under a similar title, which, however, showed no skin changes or other evidence of Von Recklinghausen's disease.

It is proposed in the following paper to describe three cases with similar pathological features, and to discuss the questions raised in reference to this group of cases.

Case 1.—Clinical history: E.R.P., a married woman, aged 23, was admitted to the Hospital for Nervous Diseases, Maida Vale, March 25, 1936, under Dr. Blake Pritchard.

The family history was negative. She had been married a year and had no child. She was in her usual health until ten months before admission to hospital, when she began to suffer from headaches, failing memory, and attacks of loss of consciousness. All these symptoms appeared at about the same time, and led to an immediate cessation of her work as a waitress. The attacks were uniform in character; she stopped what she was doing, stared vacantly in front of her, and except for slight flickering of the fingers was motionless. The attacks varied in frequency from as many as seven a day to a day of freedom. Headache followed the attacks, but soon began to come at other times and more frequently as the illness progressed. She was easily excited, complained of her poor memory for recent events, but continued her housework up to the date of admission to hospital.

On examination she was found to be mentally dull, apathetic and slow in movements, of notably defective memory, especially for recent events, but able to co-operate moderately well in her examination. She showed no disorientation. The speech function was normal. There was bilateral papillœdema of about 4-5D. In other respects physical examination was wholly negative; the reflexes, sensation, and the motor system all being normal. The cerebrospinal fluid was under a pressure of over 300 mm., but was normal in all respects. The Wassermann was negative in the blood and cerebrospinal fluid. The lumber puncture led to symptoms of a cerebellar pressure cone. Ventriculography by Mr. McKissock showed general narrowing of the bodies of both ventricles, but the patient died before a right temporal decompression could be performed.

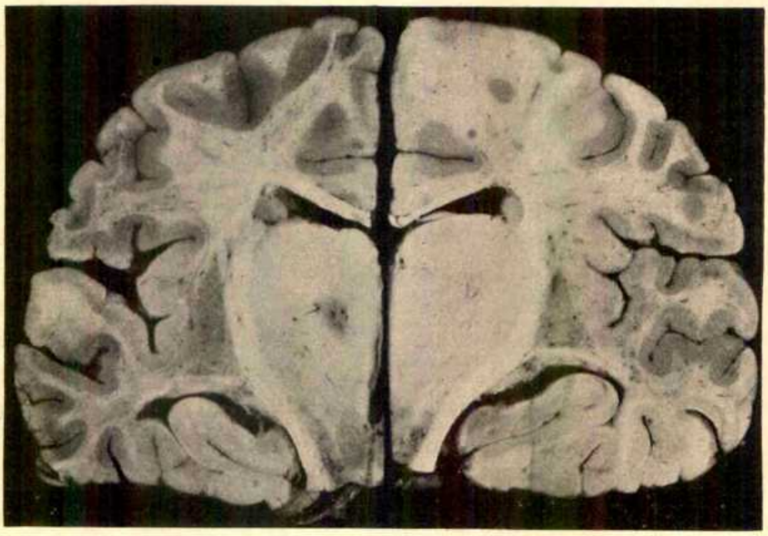

FIG. 1. *Case 1.*—Vertical section through the brain (anterior view) showing the enlargement and pallor of the thalami, the enlargement of the hippocampus, and the pallor and widening of the cerebral cortex in circumscribed areas.

Post-mortem examination.—The brain only was available for examination. It weighed 1,340 grm., and of this the cerebral hemispheres weighed 1,190 grm. A large cerebellar pressure cone was present, and the convolutions were slightly flattened. The cortex of the under surface of frontal and anterior temporal lobes was granular and irregular, and from it the arachnoid and blood-vessels stripped less easily than normal. In places the granulations were so coarse that they overlapped branches of the middle cerebral artery, and generally the blood-vessels indented the cortical surface, leaving their pattern imprinted thereon when removed. This abnormal granularity extended into the island of Reil and along the margins of the posterior ramus of the Sylvian fissure and also along the cingulate gyrus. It was symmetrical in its distribution in the two hemispheres.

The brain was sectioned vertically, revealing a diffuse pathological change throughout the greater part of the cerebral hemispheres (fig. 1). The thalami were generally enlarged, pale, and firmer than normal, causing narrowing of the lateral ventricles, and flattening of the hippocampus and hippocampal gyri. The massa intermedia was also enlarged and firm. In the cerebral cortex there was pallor and enlargement of the grey matter, with consequent loss of contrast between it and the white matter, and the distribution of these changes corresponded closely with that of the surface granulation already described. They were, however, most severe in the anterior parts of the temporal lobes, where the cerebral tissue as a whole was softer than normal, and the fissures increased in depth. The caudate and lenticular nuclei appeared normal to the naked eye except that the under part of the left caudate nucleus in its anterior part was paler, larger and softer than normal. The upper part of the mid-brain was also similarly involved, but the pons medulla and cerebellum and the walls of the ventricles showed no abnormality to the naked eye.

Microscopical examination revealed a diffuse and very symmetrical cellular overgrowth throughout wide areas of the cerebral hemispheres. This was associated with a varying new formation of glial fibres and secondary changes in the essential nervous elements, which were, however, slight in comparison to the degree of the new cell formation. The detailed changes will now be described, first in the thalamus, then in the anterior region of the temporal lobes, after which their distribution throughout the cerebral hemispheres and brain stem will be followed.

Thalamus.—In the thalamus the new growth was formed by cells with round, oval, and also elongated nuclei whose size and granular chromatin structure in general resembled that of neuroglial nuclei. There was considerable variation in the density of the chromatin network ; the nuclear membrane was well defined, and no cell body was seen with ordinary nuclear staining. There were all variations in shape between completely round and pure rod-like nuclear forms, but oval and smoothly elongated forms predominated, and alterations in the thickness of the latter along their length produced bizarre nuclear shapes. The cellular overgrowth was fairly evenly and diffusely spread throughout the thalamus, but it was condensed around the medium-sized blood-vessels where strands of elongated nuclei were found running parallel to their long axis. There was also irregular clumping of nuclei round the nerve cells.

A great overgrowth of neuroglial fibres accompanied the new cell formation. This formed a dense network throughout the whole thalamus, with striking condensations along the blood-vessels, either parallel or more irregularly arranged. There was enlargement of the perivascular spaces, and in places the adventitia of the vessels was adherent to the surrounding gliosis, while glia-like cells were found infiltrating the outer vessel coats. Hæmorrhages into the outer layers of the vessel sheaths, between the vessel and the surrounding brain tissue, and sometimes within the latter, were frequently observed.

It was found very difficult to stain the cells of the new growth by impregnation methods. Globus' modification of Cajal's gold chloride method, the fourth variant of Achúcarro's tannin silver method, and Davenport's silver stain were used unsuccessfully, but Hortega's silver carbonate method for astrocytes revealed that they consisted of unipolar and bipolar spongioblasts and astrocytes. Unipolar spongioblasts with rounded, small cell body, and short indefinite process were not numerous. The bipolar spongioblasts formed a larger part of the growth, as the elongated nuclei belonged for the most part to cells of this type. The protoplasm stained a light brown, was small in amount, and tailed off at both ends of the cell into a long fibre process, the exact limits of which could not be traced in any one field. The astrocytes varied very much in size, shape, and form. In some cells, especially those with irregular shaped nuclei, there was very little cell protoplasm, and the cell processes were short, whereas in those with oval or rounded nuclei the cells more closely resembled mature astrocytes. The irregular shaped astrocytes appeared to be transition stages between the spongioblasts and the more mature astrocytes. In all cells the nuclei were darkly granular and heavily impregnated (fig. 2*a*).

This cellular and neuroglial overgrowth did not produce severe alteration in the essential nervous elements of the thalamus. There was no gross reduction in the number of the nerve cells but they appeared more widely separated than normal and contained a few large droplets of fat which stained reddish yellow with Scharlach R. In myelin preparations the internal capsule was darkly stained and the thalamus was only slightly paler than normal, and these also showed that the cellular overgrowth round the blood-vessels gave rise to the displacement of the myelinated fibres adjacent to the vessels as is illustrated in fig. 3.

Anterior temporal lobe.—In this region the changes were typical of those affecting wide areas of the cerebral cortex. The density of the cellular overgrowth was greatest underneath the pia (fig. 4), where bundles of elongated or oval nuclei lying in a fibrillar matrix were placed either in a horizontal, vertical or oblique direction. The arrangement was not always regular, and masses of cells intermingled with the strand-like bundles produced a very varied appearance. The overgrowth extended upwards underneath the pia, forming nodular or wart-like elevations, completely irregular in shape and form, on the cortical surface. In many places it had broken through this membrane, and become adherent to the outer wall of the vessels. These were the microscopical appearances corresponding to the granularity of the cortex observable by the naked eye. Hæmorrhages had occurred into the thickened leptomeninges and between the pia and the cortex. In the deeper parts of the molecular layer and throughout the cellular layers of the cortex the overgrowth was diffuse and irregular. In some places, however, the nuclei were clumped round the nerve cells, and cellular strands were prolonged from the subpial zone along the blood-vessels right through the cortex, and even into the medulla (fig. 5). In the subcortical zone the nuclei were round and perhaps smaller than those in the cortical layers, while the cellular increase gradually disappeared in the depths of the white matter. Numerous small hæmorrhagic foci were present in both the grey and white matter, and irregular cavities also occurred in these structures. Two factors seemed to play a part in their production, enlargement of the perivascular spaces, and the absorption of the hæmorrhages.

The new growth underneath the pia was composed mostly of strands of bipolar cells associated with dense piloid masses of fine glial fibres, but in some parts the gliosis was a dense network, and numerous astrocytic cells were present. The latter predominated in the deeper parts of the molecular layer. In the cortical cell layers

PLATE V.

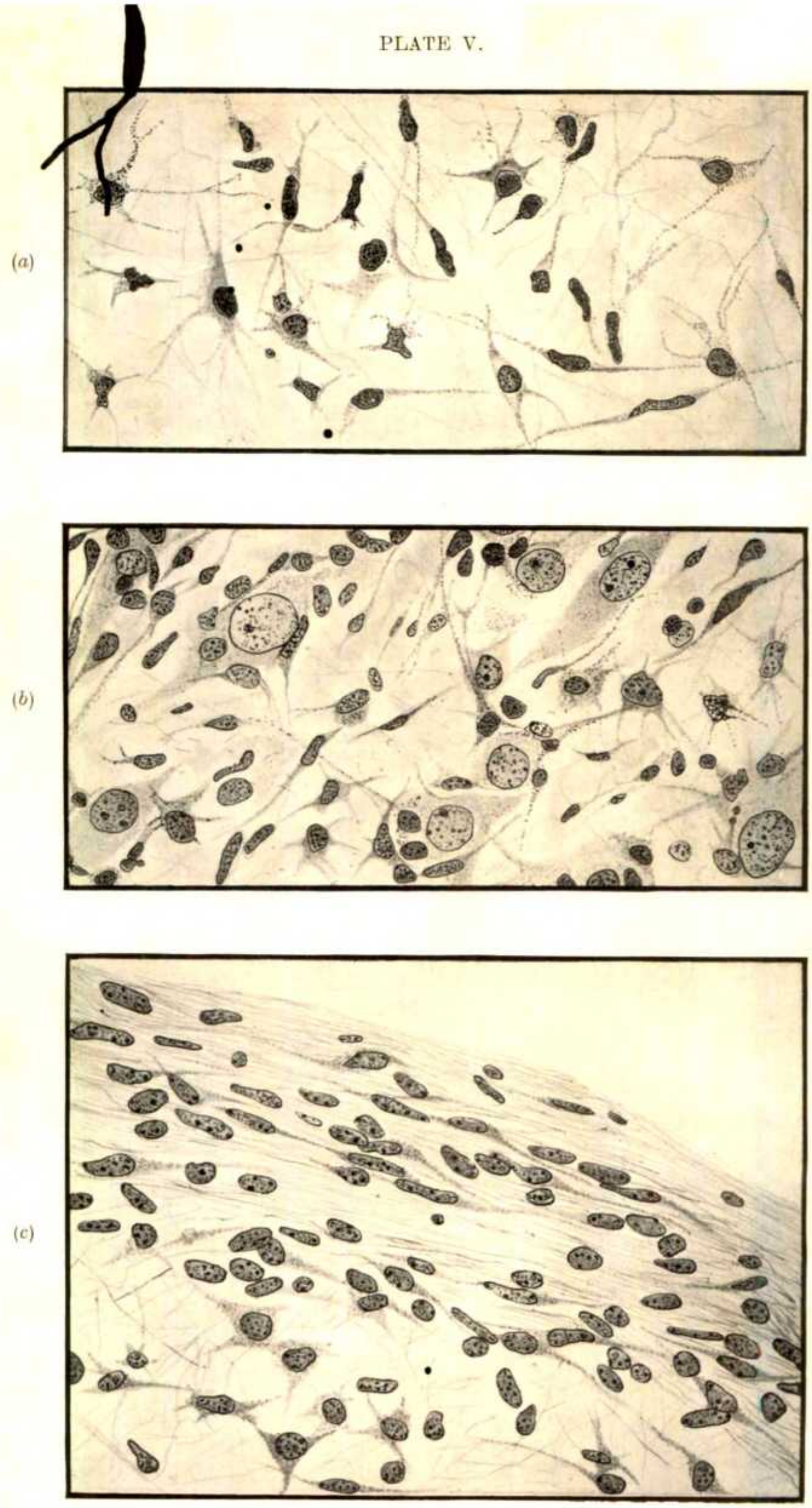

FIG. 2.

To illustrate paper by Samuel Nevin.

PLATE VI.

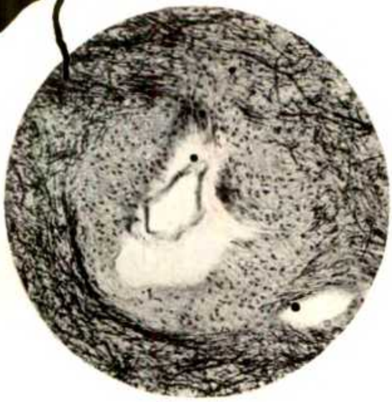

FIG. 3.

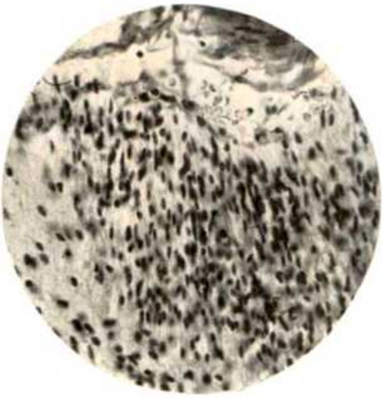

FIG. 4.

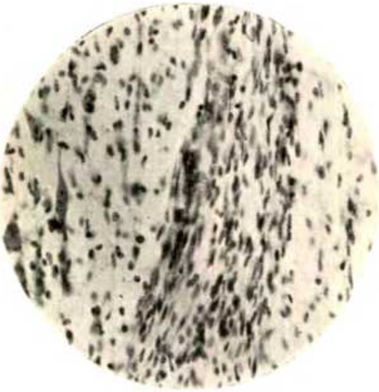

FIG. 5.

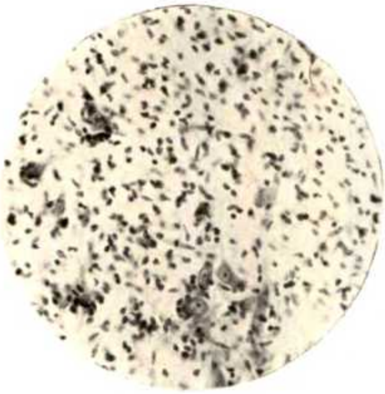

FIG. 6.

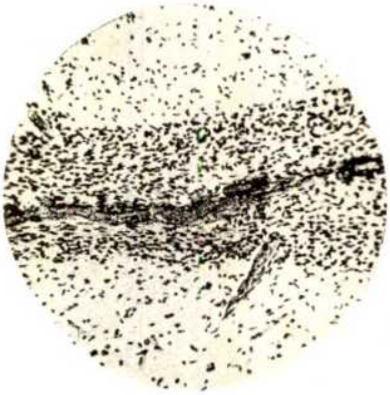

FIG. 7.

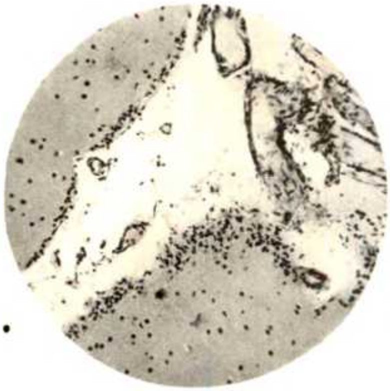

FIG. 8.

To illustrate paper by Samuel Nevin.

the glial overgrowth was a very loose open network formed of large thick fibres which stained better with iron hæmatoxylin than with victoria blue, and unipolar, bipolar, and astrocytic types of cells were scattered fairly evenly throughout the cortex (fig. 2 *b* and *c*). Bipolar forms predominated in the cellular strands along the blood-vessels. In the subcortical white matter the gliosis was a fine dense network staining darkly with victoria blue, and the cells were mainly astrocytic with some variation in size and shape. This variation in the fibre production in the grey and white matter seemed to reflect the normal difference in the neuroglia in these structures. It is also interesting to note that Nissl preparations showed faint staining of the cell processes of the bipolar spongioblasts.

This new growth resulted in considerable loss of nerve cells, especially the granular cells. There was alteration and distortion in the arrangement of those remaining, so that the cortical layers were not recognizable in the areas of greatest growth (fig. 6). The residual nerve cells were lying at all angles to the surface of the cortex, some even being actually reversed in position, and the dendrites also shared in the distortion, being curved in unusual manners. Such cells were more fusiform than normal, and they contained small accumulations of fat, staining reddish yellow with Scharlach R at the base of the cell or extending round the nucleus. There was also degeneration of the myelinated fibres in the cortex and subcortical white matter, but the tangential fibres even in the most affected areas were still to be seen, although widely separated amidst the cellular overgrowth.

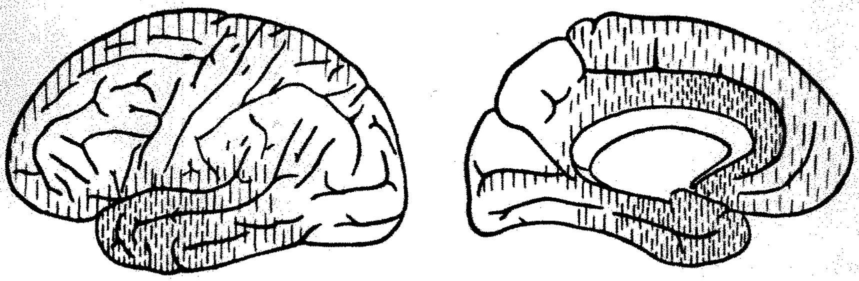

FIG. 9. *Case 1.*—Diagram showing the distribution of the cellular overgrowth in the cortex.

General Distribution of the Microscopical Changes.—The severe cortical changes, leading to gross distortion of the nerve cell layers, were confined to a small area of the anterior and medial aspect of the temporal lobes. The more widespread changes, the distribution of which is illustrated in fig. 9, were less severe. Although there was still considerable loss of nerve cells the cortical layers were still recognizable, and the diffuse overgrowth in the deeper parts of the cortex was in striking contrast to the dense subpial infiltration (fig. 7). The changes gradually diminished towards the normal cortex, where the subpial overgrowth became reduced to a layer a few cells thick and there was only a slight excess of irregular and elongated neuroglial cells in the deeper layers.

The new growth spread from the affected cortical areas through the basal ganglia, and was continuous with that in the thalamus. It was, however, much less in the basal ganglia, and the gliosis was greater in the fibre bundles and internal capsule than in the grey matter. The optic chiasma was intensely gliosed and here dense piloid masses of fibres were found running along the septa between the nerve bundles and spreading as an open network irregularly throughout the whole structure. The margin of the mid-brain was encircled by a slight subpial overgrowth, while the dorsal part of this structure contained a diffuse cellular and glial proliferation. This dorsal infiltration extended down the pons and medulla to the upper part of the spinal cord where slight changes were found in the grey matter, especially in the posterior intramedullary root zone. The general structure of the cerebellum was normal, but occasional foci of subpial overgrowth similar to that seen in the cerebral cortex were found on the anterior and inferior surface (fig. 8). The fourth nerve was sectioned at the side of the mid-brain, and showed definite involvement of the nerve by bundles of new cell formation, intensely fibrillar, and staining with neuroglial stains similar to the subpial overgrowth. This seemed to have grown from the brain stem out into the nerve. A similar appearance was observed at the junction of the upper posterior cervical roots with the spinal cord.

Summary of Case 1.

The case was characterized clinically by symptoms of gradually increasing intracranial pressure associated with general mental dullness, marked failure of memory, and epileptic attacks.

The pathological process consisted in a new growth of spongioblasts and astrocytes, irregular and variable in size, shape, and form, throughout wide areas of the cerebral cortex, the basal ganglia, thalamus and upper part of the brain stem. This new growth was implanted on the normal structure of the nervous system, and produced comparatively slight secondary changes in the essential nervous elements. The distribution of the cellular overgrowth was not completely irregular, but bore a definite relationship to the normal structure of the nervous system. In the cortex it was greatest underneath the pia mater, where the predominant type of cell was a bipolar spongioblast with dense fibre formation. In the cellular layers of the cortex the overgrowth was more diffuse and less densely arranged. The cells were spongioblasts and astrocytes in irregular arrangement, and the fibre formation was a coarse, wide open network difficult to stain. The subcortical zone of the white matter was more affected than the deeper parts of the white matter, and here the growth was mainly astrocytic, with a dense fine glial network. In the thalamus a spongioblastic and astrocytic growth with dense fibre formation was present.

Case 2.—Clinical History: H. S., an unmarried woman, aged 54, was admitted to the Hospital for Nervous Diseases, Maida Vale, September 12, 1936, under Dr. Russell Brain.

The family history was negative. The patient had been subject to epilepsy all her life. The attacks were infrequent and mostly minor in character, but from time to time major attacks occurred. She was in her usual health up to four years before admission to hospital, when it was observed that she was losing her initiative and her interest in life generally. A year later these symptoms were more obvious, and she had become completely self-centred and emotionally unstable. The advance of the illness continued to be slow up to six months before her death, when a rapid change for the worse took place. The patient's mental state deteriorated rapidly. She became completely apathetic, with no inclination to do anything but feed herself, and she also became incontinent of urine and fæces, and at times hid her excreta under the cushions and the piano. Failure of memory, according to the relations, was not an outstanding feature, although it was undoubtedly present with the gross mental deterioration. About this time progressive weakness of the right arm and leg was first noticed. She was admitted to hospital in a very drowsy and stuporose state, from which she could just be roused. Early papillœdema was present in both eyes, greater on the right side. There were extensive areas of pigmentation on the neck and upper limbs, similar to the cutaneous pigmentation of Von Recklinghausen's disease. There was complete right-sided flaccid hemiplegia. The cerebrospinal fluid was not examined, and X-rays of the skull were not taken. She gradually became unconscious, and died twenty-four hours after admission to hospital.

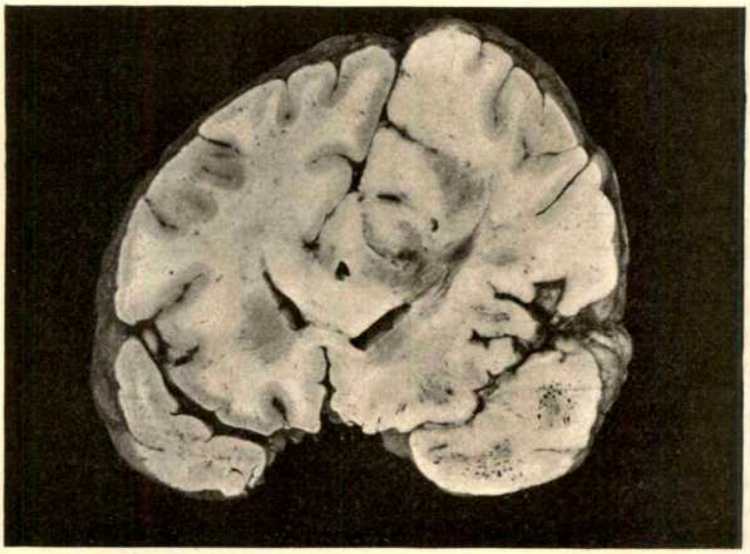

FIG. 10. *Case* 2.—Vertical section through the brain showing the enlargement of the left hemisphere, the severe changes round the left cingulate sulcus, the loss of contrast between the grey and white matter, and the honeycombing of the white matter.

Post-mortem examination.—The brain only was available for examination. A small firm greyish-white tumour, about the size of a hazel nut, was present in the suprapituitary region posterior to the stalk of the pituitary. The brain weighed 1,093 grm., and of this the cerebral hemispheres weighed 957 grm. The left cerebral hemisphere forwards from the fissure of Rolando was larger than the right. There was a moderate cerebellar pressure cone, and a herniation of the uncus on both sides, that on the left side being larger, and also somewhat rough and nodular. The cortex on the under surface of the frontal lobes, especially on the left side, was somewhat granular in appearance, and less smooth than normal. There was a slight purple discoloration of the margins of the posterior ramus of the left Sylvian fissure for a distance of about one and a half inches from its commencement. Similar areas of discoloration, only darker, were found on the left middle frontal convolution about its centre, and on the anterior part of the medial aspect of the superior frontal convolution.

The brain was sectioned vertically, and this revealed a diffuse pathological change throughout wide areas of the anterior parts of the hemispheres (fig. 10), consisting in increased depth of the cerebral cortex, loss of normal contrast between the grey and white matter, and a honeycombed appearance of the subcortical white matter. The anterior part of the left cingulate sulcus was greatly increased in depth, and the surrounding grey matter was two to three times its normal width. It was also paler and softer than normal, and had a somewhat translucent appearance. In the grey matter at the foot of the sulcus, and about the level of the genu of the corpus callosum there was a small area of darker discoloration, which felt gritty to the touch owing to foci of calcification. The subjacent white manner was somewhat dark, and in one or two places irregular fissures had appeared in the tissue.

Similar, only less severe, changes were present over the whole inferior and medial surface of the left frontal lobe. They extended backwards involving the anterior part of the temporal lobe, the island of Reil, and the margins of the posterior ramus of the Sylvian fissure, which were adherent to one another. In these areas the underlying white matter had a honeycombed appearance, especially in the subcortical zone. Where this appearance of the white matter was most marked the pallor of the grey matter was greatest, and in such areas the line of demarcation between these structures was not visible. In the right hemisphere the changes were much less extensive and confined to a small area round the anterior part of the cingulate sulcus, and in the anterior part of the temporal lobe. The basal ganglia were normal in appearance apart from slight pallor of the antero-lateral parts of the left lenticular and caudate nuclei. The anterior part of the corpus callosum was broader than normal, causing some outward and downward displacement of the anterior horns of the ventricles. No changes to the naked eye were visible in the thalamus or posterior part of the hemispheres, nor in the cerebellum or brain stem.

Microscopical Examination revealed that the naked eye pathological changes were produced by a diffuse cellular overgrowth throughout wide areas of the cerebral hemispheres. This will be described in detail in sections taken from the medial aspect of the left frontal lobe, and the distribution of the changes throughout the hemispheres will then be followed.

Left Frontal Lobe.—In the grey matter surrounding the anterior aspect of the cingulate sulcus a dense cellular overgrowth, composed of cells with round, oval and irregular-shaped nuclei, extended from the surface to the subcortical white matter and obliterated practically entirely all traces of the normal cortical structure. The nuclei were darkly granular, varied much in size and shape, and no cell body was seen with ordinary stains. Underneath some parts of the cortex fibrillar bundles of elongated nuclei were seen running parallel to the surface and intermingling with fibrous tissue growth from the leptomeninges, while in other parts dense masses of rounder nuclei projected from the surface in small nodes. Here and there foci of diffuse hæmorrhage were present and the blood-vessels were adherent to the cortex and their outer walls infiltrated with cells from the surface overgrowth. The moleculer zone was filled with masses of more or less rounded nuclei, but in the cellular layers the new-formed cells were more evenly arranged throughout the tissue. Occasionally they occurred in clumps of three or four, or in short chains. Amitotic division could be seen with the formation of two very unequal nuclei. They practically filled the whole field, but isolated nerve cells were found throughout the whole depth of the cortex (fig. 12). The capillaries were very congested, and irregular masses of calcification were found in relation to the small blood-vessels, the walls of which showed fibrous thickening and endothelial proliferation. In the subcortical white matter the nuclei were smaller and rounder and very evenly arranged.

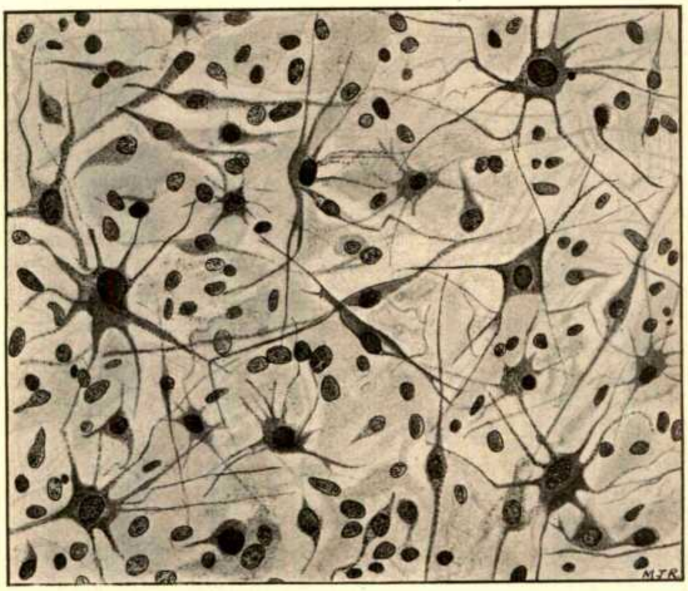

FIG. 11. *Case 2.*—Camera lucida drawing from a preparation of the grey matter beneath the left cingulate sulcus stained by Hortega's silver carbonate method for astrocytes. The varied size and shape of the astrocytic and spongioblastic cells are illustrated.

Impregnation by Hortega's silver carbonate method for astrocytes revealed the neuroglial origin of the new growth and all varieties of cells from immature spongioblasts to fully developed astrocytes were found. In the cellular layers of the cortex there were numerous large astrocytes of varying shape and form with large protoplasmic body and long coarse processes, and also large bipolar cells with terminal processes. These cells formed, however, only a small part of the overgrowth, because in the meshes of the fibrillar network formed by their processes lay numerous small unipolar and bipolar spongioblastic cells. Some of these showed a very sharply outlined cell body with fine terminal processes, but the majority showed a lightly stained body, with a coarse and faint cell process which could not be traced very far from the parent cell body. Many of the nuclei, however, showed no recognizable cell body, most likely owing to the immaturity of the cells (fig. 11). The appearance was not, however, uniform throughout the whole depth of the cortex. In the subpial zone there were more numerous mature spongioblasts and astrocytes of medium size with long thick processes extending into the deeper parts of the molecular layer, while in the white matter small astrocytes predominated. The victoria blue stain for neuroglial fibres reflected the difference in cellular forms in the different cortical layers. A dense marginal gliosis of varying thickness filled the outer part of the molecular layer from which long thick processes extended inwards. In the cortex itself there was only an open network of thick pale fibres except along the small blood-vessels where parallel bundles of fine dark fibres were present (fig. 13). In the subcortical white matter, however, the gliosis was a dense fine network, with special condensations round the blood-vessels, so that there was a striking contrast between the glial formation in the grey and white matter (fig. 14).

The cellular overgrowth just described led to considerable but not complete destruction of the essential nervous elements. Myelin stains showed pallor of the subcortical zone, but isolated fibres with varicosities on their course occurred regularly in the midst of the dense cellular overgrowth. Also in the cortex fragments of the vertical and horizontal fibres were still to be seen. Residual nerve cells, mostly the large pyramidal cells, were also found regularly throughout the cortical layers. In most of these no Nissl granules were seen, but a greenish granular appearance of the protoplasm was present, due to lipoid accumulations in the cells at one or other pole, or right round the nucleus. This stained reddish with Scarlach R. Some of the pyramidal cells had become rounded or fusiform, and elongated in a direction vertical to the cortical surface, while in some the dendrites were twisted and curved in unusual manners.

The Microscopical Distribution of the Cellular Overgrowth.

This was much greater than the area of macroscopical change. On the left side the new growth was most severe round a line drawn from the cingulate gyrus to the island of Reil, and except for the region round the Sylvian fissure the medial areas of the hemisphere were more severely involved than the lateral. The entire frontal lobe was more or less involved, but in the parietal and temporal lobes the changes gradually disappeared posteriorly so that they were restricted at the termination of the Sylvian fissure to a small area of the upper margin of the fissure. In the anterior and medial aspects of the left temporal lobe the new growth was widespread and intense. In the right hemisphere it was much less extensive and more closely confined to the area of macroscopic change. There were no definite changes in the thalami, but the upper part of the brain-stem was involved round the central canal.

In following the distribution of the new growth, all degrees of pathological change were found, from an area of the cortex where only a few remaining nerve cells and fibres were present in the midst of a dense new cell formation, to an area where the structure of the cortex appeared normal and only a few pathological cells were scattered around and between the nerve cells. A characteristic feature in the less affected areas was the clumping of small-sized astrocytes and spongioblasts around the nerve cells (fig. 15).

Even in the less affected areas the subjacent white matter generally showed intense gliosis, and this was especially marked on the medial surface of the right frontal lobe, where there was not, however, a corresponding degree of demyelinization. In the left

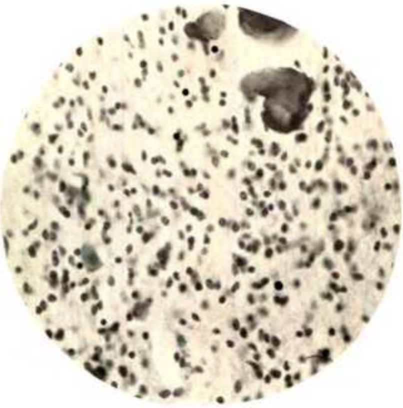

FIG. 12.

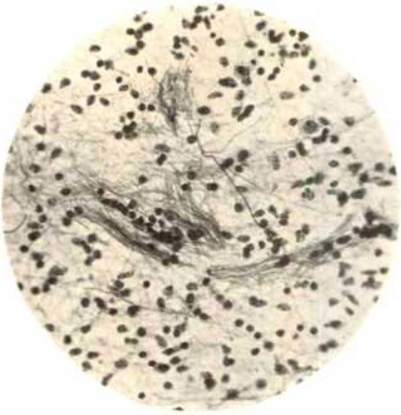

FIG. 13.

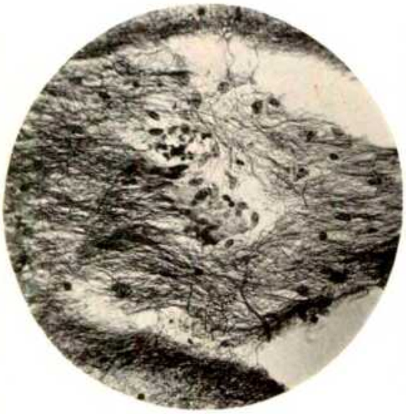

FIG. 14.

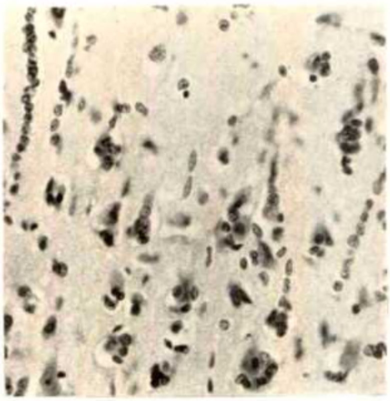

FIG. 15.

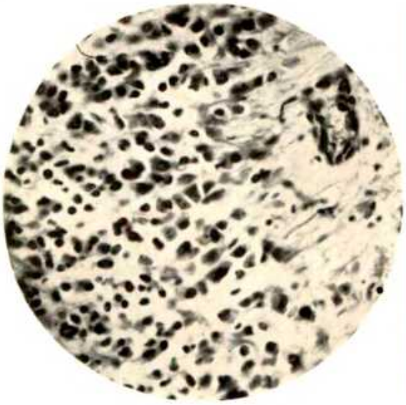

FIG. 16.

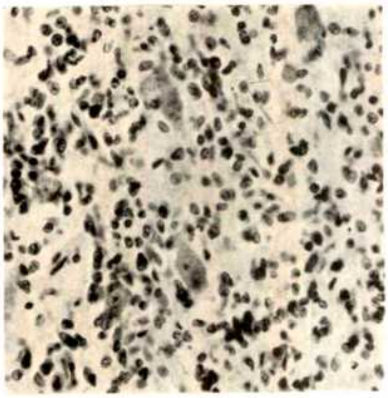

FIG. 17.

To illustrate paper by Samuel Nevin.

hemisphere the gliosis in the white matter had spread widely throughout the anterior two-thirds of the hemisphere, producing demyelinization, and oval and elongated fissures occurred in the sclerosed tissue. This cavitation was the cause of the honeycombed appearance in the brain observable with the naked eye. These cavities sometimes contained vascular channels consisting only of an endothelial lining and a fibrous tissue coat which varied very much in thickness, and was in some places adherent to the glial margin of the cavity. In the anterior part of the left temporal lobe the gliosis in the white matter was very intense, so that in some places it spread outwards into the cellular layers of the cortex as a dense network. The adherence of the cortical margins of the Sylvian fissure was produced by densely fibrillar and cellular bundles passing in all directions round the Sylvian vessels, uniting these to each other and to the cortex. Below the fissure, despite the continuity of tissue, the overgrowth was slight in comparison with that in the superior margin.

The dense gliosis of the white matter of the left frontal lobe stopped abruptly at the margin of the caudate and lenticular nuclei. In these structures which showed a moderate cellular overgrowth the gliosis was a loose open network, with fibrillar accumulations along the small blood-vessels exactly similar to the condition already described in the cortex of the anterior part of the cingulate gyrus. Also, in the anterior part of the internal capsule, the anterior commissure, the optic chiasma and the fornix, the fibrillar nature of the new growth was in striking contrast to that found in the adjacent cellular areas of the nervous system. There was no demyelinization in these structures.

The walls of the anterior parts of the lateral ventricles were intact, but they were surrounded by a thick gliosis, which was irregularly cellular, and contained large accumulations of ependymal cells and numerous corpora amylacea.

The overgrowth in the brain stem spread outwards from the central canal and affected the dorsal part of the mid-brain. It was intensely fibrillar and piloid masses of glial fibres projected into the lumen of the canal. There was also marginal gliosis round the medulla and upper part of the spinal cord. In these latter areas the neuroglial nuclei showed greater variation in size and shape than normal, but there was no definite increase.

In the posterior parts of the cerebral hemispheres, clearly uninvolved in the general overgrowth, foci of marginal gliosis were found in different places associated with groups of neuroglial cells in the subjacent molecular layer. The neuroglia in the cellular layers did not appear increased, but the variation in shape and form of the astrocytes appeared greater than normal, while in the white matter perivascular foci of neuroglial cells were sometimes found.

Focus of Anaplastic Tumour Formation in the left frontal lobe.

In the white matter underneath the superior frontal sulcus, anterior to the genu of the corpus callosum, an oval area of complete demyelinization three millimetres wide and six millimetres broad was found. The anteroposterior length of the area was not determined, but it was not much more extensive than the breadth. This was caused by a new growth of elongated, bipolar or pyramidal cells with round or oval nuclei arranged irregularly or in a radiating manner round the blood-vessels. Lightly-stained cell processes connected with the thin fibrous tissue sheath of the vessel walls, but not other cell processes or neuroglial fibres were stained (fig. 16). This focus of cellular overgrowth, which could be classified as a spongioblastoma multiforme, was quite distinct from the more widespread changes because it had completely replaced the normal nervous structure and formed its own blood supply, and was clearly spreading as a single tumour from its point of origin. The cells in the tumour bore little, if any, resemblance to neuroglial cells, mature or undeveloped, and were stained to some extent by iron hæmatoxylin and van Gieson, and Davenport's silver stain, while the cells forming the general overgrowth were unstained by these methods, and their derivation from neuroglial cells was clear.

Developmental abnormalities and general changes in the nerve cells.

In the white matter underneath the calcarine fissure there was a slit-like cavity lined by ependymal cells surrounded by a mass of dense gliosis. Also in the upper part of the spinal cord the anterior fissure was absent over the first cervical segment, so that nerve cells were found underneath the anterior surface, and the anterior columns were spread over the lateral surface of the cord. At this level there was also cavitation along the posterior septum.

The nerve cells in the thalamus, brain stem and uninvolved areas of the cortex very frequently showed fatty accumulations in one part or other of the cell body. The significance of this pathological change was not clear. It was also very difficult to decide if slight alterations in the size and form of the larger pyramidal nerve cells in uninvolved cortical areas were greater than normal, but detailed studies of the architectonics of the cerebral cortex were not made.

The Suprapituitary Tumour.

Microscopically this tumour had the structure of a neurofibroma in which there was also present numerous thick-walled blood-vessels of varying size. In parts of the tumour these abnormal vessels were so numerous, and filled so much of the field, that they could very well be regarded as a composite part of the tumour, which might therefore be more adequately described as an angioneurofibroma.

Summary of Case 2.

The case was characterized clinically by a life history of epilepsy, four years' history of mental deterioration, failure of memory and character changes. Pigmentary skin changes as in Von Recklinghausen's disease were present. Death followed the development of symptoms of increased intracranial pressure and gross right-sided hemiplegia. The pathological process consisted in a new growth of spongioblasts and astrocytes, irregular and variable in size, shape and form, throughout wide areas of the anterior parts of the cerebral hemispheres, especially on the left side and involving also the brain stem. This new cell formation was superimposed upon the essential nervous elements, producing in these structures severe secondary changes in the areas of greatest growth. It was accompanied by a varying gliosis, which was not completely irregular, but bore a definite relationship to the normal structure of the nervous system. In the white matter this was a fine dense network, arising from small astrocytic cells, whereas in the grey matter the glial increase was a coarse open network, formed for the most part by the processes of large astrocytic and spongioblastic cells, except along the small blood-vessels, where bundles of fine fibres were also present. An anaplastic focus of true tumour formation was found in the midst of the general cellular overgrowth, and a neurofibroma was also present in the suprapituitary region.

For the following case I am indebted to Dr. Gordon Holmes. The notes are from the routine clinical and pathological records of the National Hospital.

Case 3.—Clinical history: L. T., a man aged 27, was admitted to the National Hospital, May 7, 1909, under Dr. Gordon Holmes.

The family history was negative. As a youth he was subject to fainting attacks, the exact nature of which was not clear. At the age of 14 he suffered a blow on the head, and was unconscious for two hours. Otherwise he was well up to two and a half years before admission to hospital.

At this time he began to complain of epileptic attacks, headaches and loss of memory. The epileptic attacks, which were infrequent but generally severe, were preceded by a cramping, tingling pain in the right side of the face just before consciousness was lost, and followed by a transitory weakness of the right side. The headaches were very variable, and often localized behind the eyes. The symptoms gradually progressed up to admission to hospital. Examination revealed a marked failure of memory for both recent and remote events, and also some difficulty in remembering the names of objects. There was no mental or speech disturbance. Papillœdema developed under observation and apart from this the only abnormal physical signs were a slight lower right facial weakness, and a slight loss of sense of position in the right arm and leg.

In a two-stage operation Sir Victor Horsley performed a left cerebral decompression on the clinical diagnosis of a left parieto-temporal tumour. No definite tumour formation was located, and he was discharged fairly well and able to walk about, on July 5, 1909. This improvement was only maintained for a short time, and soon he began to deteriorate rapidly. Fits occurred with greater frequency and many minor attacks, consisting only of momentary loss of consciousness, took place, and he was again admitted to hospital on May 2, 1910, in a completely inco-operative state, with a gross right hemiplegia and hemianæsthesia to pin-prick. There was a large left-sided temporo-sphenoidal hernia. Death took place thirteen days later.

Post-mortem examination.—The right temporo-sphenoidal lobe of the brain was enlarged and bulky, and seemed to compress the right optic nerve and the right side of the optic chiasma. On section a large circular reddish soft degenerate area was found in the anterior part of the right cerebral hemisphere, underlying the third right frontal convolution and the island of Reil. Also in the right temporo-sphenoidal lobe the cortical grey matter was not sharply differentiated from the underlying white matter, and in this area there were also a few scattered hæmorrhages. The anterior part of the corpus callosum and the fornix were somewhat enlarged, and the former presented a honeycombed appearance.

Microscopical examination.—This revealed that the naked eye changes were produced by a diffuse cellular overgrowth which involved not only the softened area of the right frontal lobe, but also spread throughout wide areas of the anterior parts of both hemispheres, and also the corpus callosum. It was composed of round, oval, and elongated nuclei with granular chromatin network, resembling neuroglial nuclei, only somewhat denser. The nuclei varied very much in size and shape, and also in the density and manner of their arrangement in different areas (fig. 17). In the left parietal region the new growth was of fairly even density throughout the whole thickness of the cortex. Numerous well-preserved nerve cells were seen, but recognition of the cellular layers of the cortex was not possible. Mallory's phosphotungstic hæmatoxylin stain revealed neuroglial fibres, forming a dense network subpially and in the white matter, but the fibres were coarse and widely separated in the grey matter. Astrocytes and bipolar cells of varying size and form could be made out everywhere, but these formed only a small part of the actual new cell formation, which consisted mainly of smaller cells, the actual structure of which was not determined. A similar appearance was seen in the left temporo-sphenoidal lobe. In the inferior region of the frontal lobes the new growth was very dense, the nuclei more elongated and collected in parallel bundles in the subependymal region and under the pia. In the softened area of the right frontal lobe the nuclei were on the whole small and rounded and densely packed. Although it is not possible to present full pathological details of the case, the very clear clinical and pathological resemblance to Case 2 justifies its inclusion in this paper.

Summary of Case 3.

The case was characterized clinically by epilepsy, failure of memory, and symptoms of increased intracranial pressure which eventually proved fatal. Pathologically there was present a diffuse cellular overgrowth throughout wide areas of the anterior parts of the cerebral hemispheres. This was formed of astrocytic and spongioblastic cells, and was superimposed upon the essential nervous structures, gradually replacing them. The accompanying gliosis was not entirely irregular, but greater subpially and in the white matter, and less in the grey matter.

General Discussion.

The three cases which form the subject matter of this paper have been considered examples of a similar type of pathological change in the central nervous system. There are some differences in general histological appearance, especially between the first and second cases, but these appear to be differences in the rapidity of growth, and in the size and shape of similar types of cell, and not in the essential pathological process as is shown by the following considerations. In each case a widespread overgowth of cells of neuroglial origin with similar staining reactions had superimposed itself upon the essential nervous elements, and led to secondary changes in these structures in direct proportion to its intensity; so that one found all degrees of change, from a slight general increase of the normal neuroglia, to an area resembling a circumscribed new growth. This new growth was associated with a gliosis which varied with the normal structure of the nervous system, being a dense fine network in the white matter, and a coarse open network, staining faintly with victoria blue, in the grey matter of the cortex and basal ganglia. Also, there was in all cases dense fibril formation in those sites where there is normally a condensation of fibrous neuroglia, namely, in the outer zone of the molecular layer, underneath the ventricular surface, and along the blood-vessels. The clumping of newly-formed spongioblastic and astrocytic cells round the nerve cells was also found equally in the first two cases. Other similar features were the extension of the cellular and fibrous overgrowth into the leptomeninges and the walls of the blood-vessels, producing degeneration of the vessel walls and hæmorrhages round the vessels and into the superficial layers of the cortex. Hæmorrhages and fissuring in the gliosed tissue were also present in both cases in the deeper parts of the nervous system, the former being more marked in the first case, and the latter in the second.

With regard to the nature of the pathological process, it will be quite clear that the cases cannot be regarded as straightforward examples of tumour growth and an attempt made to classify them according to their possible cell of origin. In the first place the occurrence of characteristic cellular overgrowth underneath the pia on the undersurface of the cerebellum in Case 1, and the very great variation in the cellular overgrowth from point to point in Case 2, makes it unlikely that the growth could have arisen in any one area and spread directly as a single tumour formation. The tendency also for the overgrowth in the first case to involve mostly the cellular layers of the cortex and the subcortical white matter is an important point in this respect. Further, the retention of the normal elements of the nervous system, even in areas of severe new cell formation, is much greater than is found in true tumours of the nervous system. Apart from these considerations it would be impossible to designate as a tumour formation by direct spread, an overgrowth which varies its cellular and fibre overgrowth anatomically, so that one finds very constantly a sharp distinction at the junction of the subcortical white matter and the cellular layers of the cortex. This feature seems to indicate clearly, despite the very dense cellularity in some areas which would be quite indistinguishable if considered alone from an area of rapidly growing tumour formation, that the new formed cells had not escaped entirely from the laws that govern normal growth, and that their development was influenced to a much greater extent than is usual in simple tumour formation by the normal structures where the overgrowth was taking place.

Another unusual feature in the cases was the very great variation in the form and shape of the individual cells. In one area the section could easily be labelled medulloblastoma, in another spongioblastoma with fine fibre formation or piloid astrocytoma, and in another diffuse astrocytoma. Any one, however, of these classifications of tumour growth would be quite inapplicable to the overgrowth as a whole. This varied appearance probably resulted from the differentiation of cells from immature to more mature forms to a much greater extent than takes place in a true neoplasm. Further, in the brain stem and cortical areas not involved in the general cellular overgrowth there were found abnormalities in the neuroglia which cannot be regarded as a direct spread of tumour growth throughout the nervous system.

This last observation seems to give a clue to the histogenesis of the whole overgrowth in that it probably indicates a developmental abnormality of the neuroglia generally, associated with which it is possible for the widespread cellular overgrowth to arise. The pathological process has therefore been regarded, not as a neoplasm in the strict sense of the term, but as a blastomatous malformation, in some way or other congenitally predetermined, although it is recognized that in reference to some parts of the overgrowth it may be impossible to define the boundaries between malformation and true tumour formation. This does not explain the origin of the new formed cells, whether from adult cells or from residual undifferentiated cells, nor the factors which caused the late onset of intense proliferation, but such questions are equally obscure in relation to the whole group of blastomatous malformations of the nervous system. If, however, some developmental abnormality of the neuroglia exists, it is possible that proliferative tendencies may develop in relation to this, and that a general overgrowth may arise over a widespread area, or having arisen in one area, cause its development in adjacent areas. On such a basis it is easier to understand the close relationship of the new formed cells to normal neuroglia and the gradual replacement of the nerve cells and fibres. The great capacity of the cells for differentiation, and also the variation of the cellular form and fibre development of the overgrowth depending on the surrounding tissues is more comprehensible.

It has been stated that general neurofibromatosis, affecting the peripheral nerves, is not a true neoplasm, but a diffuse fibroblastic overgrowth which may form focal manifestations resembling tumours, while in places true tumours may actually arise. The pathological process under discussion could be similarly regarded, the neuroglia in the nervous system being involved instead of the fibrous tissue in the peripheral nerves. Here, however, a much greater variety of pathological change is to be expected, because of the greater possibility of abnormal development in the neuroglia cells as compared with the fibroblastic cell.

Support for the conception that the cases under discussion are primarily blastomatous malformations is found in the study of the central changes of Von Recklinghausen's disease. It is recognized that a feature of this disease is the occurrence, mostly in the cortex, of nests of gliogenous cells, or even a diffuse increase of glia which does not essentially disturb the cortex. Gamper (1929) described changes of this category in a case of Von Recklinghausen's disease, which showed also multiple ventricular and subependymal tumours. In the medial aspect of the frontal lobes anterior to the genu of the corpus callosum he found infiltrating both the cerebral cortex and white matter a diffuse cellular overgrowth which resembled in histological details very closely the changes found in the frontal region in the second case of this paper. This abnormality would be regarded as a blastomatous new formation of neuroglial cells in various stages of differentiation, and primarily dependent on some dysgenetic factor. Wherefore it seems reasonable to suppose that such an abnormality may in some cases be the predominant type of blastomatous change and spread widely over the cerebral hemispheres.

Another case may be mentioned. Schnyder (1928-29) has described in a thirty-one year old male, a dense gliosis of the right optic nerve with numerous glial cells, resulting in considerable demyelinization and thickening of the nerve. A diffuse glioma of the hypothalamus and neurofibromatous tumours on the 3rd cervical nerve and 9th intercostal nerve were also present. The intense gliosis of the optic nerve was very similar to the gliosis of the optic chiasma which was present in the first two cases of this paper. It is therefore significant that in the second case of this paper there were present skin changes such as are found in Von Recklinghausen's disease, and also a neurofibromatous tumour in the suprapituitary region, features which in themselves would justify one in regarding the widespread central changes as congenitally predetermined.

Correlation of the Cases with similar ones in the literature.

The similarity of the pathological changes found in the cases of Landau, Schwartz and Klauer, Hildebrandt, and Cassirer and Lewy especially with those in the second case of this paper, is very clear, and each of these authors regarded the pathological process as a widespread blastomatous overgrowth of neuroglial cells which had arisen in a congenitally abnormal tissue, or was dependent on a tendency to tumour formation affecting a wide area of the glial system.

Foerster's case is, however, more closely related to the first case of this paper, in that the distribution of the cellular overgrowth was very similar, and the cells were more elongated and rodshaped. The macroscopical appearances of the cut brains were also similar. This case, however, showed no new formation of glial fibres, and no processes from the cells could be stained. Foerster therefore regarded the new formed cells as lemnoblasts, or precursors of sheath of Schwann cells, and called the disease central diffuse Schwannosis. It would appear very difficult to establish such a conception for a diffuse new growth throughout wide areas of the central nervous system. As the general characteristics of the pathological process in Foerster's case were very similar to Case 1 in this paper, it seems likely that the cells were really undifferentiated neuroglial cells, and that the case is similar to the group under consideration. This similarity is further evidenced by the presence of typical skin changes of Von Recklinghausen's disease in Foerster's case. The very early age of the onset of the disease may bear some relation to the undifferentiation of the cellular overgrowth.

In Santha's case, the child also was very young, being only 9 years of age. Santha also found some unipolar and bipolar spongioblast-like cells and a defective development of the macroglia. He regarded the main new growth, however, as composed of lemnoblasts; but, owing to the presence of spongioblast-like cells, stated that the lemnoblasts are in genetic relationship to the macroglia, and not to the oligodendroglia. It would seem more probable that the cellular overgrowth was in its entirety neuroglial, and that the pathological process is identical with that already discussed, but is nevertheless distinctive in that the new formed cells were for the most part undifferentiated abnormal glial cells.

It will be clear from the above discussion that one considers the cases of this paper, and those collected from the literature, as forming a distinct group, closely related pathologically, but with wide variations in microscopical details. The pathological relationship consists in a dysgenetic abnormality of the neuroglial system of the brain, whereby the tendency to a widespread blastomatous neuroglial malformation exists. The factors which will cause this to appear at one or other decade of life are unknown. The cases are primarily a blastomatous malformation, but in the areas of most dense overgrowth it may be impossible to say where malformation ends and true tumour formation begins. Gliomatosis cerebri seems the most suitable name for the entire group of cases. They are clearly closely related to Von Recklinghausen's disease, and appear analogous to the cases of widespread neurofibromatosis of the peripheral nerves, where the cellular overgrowth might be more correctly regarded as a blastomatous malformation than as a true tumour formation.

RELATIONSHIP OF GLIOMATOSIS CEREBRI TO OTHER FORMS OF TUMOUR FORMATION.

While the cases are thus closely related, on the one hand to the well-recognized group of blastomatous malformations to which the name of Von Recklinghausen's disease has been given, they are also related, on the other hand, to certain types of localized tumour formation in the central nervous system. These are glioma of the optic nerve, glioma of the pons or pontine hypertrophy, and diffuse glioma of the optic thalamus ; tumours which are very difficult to classify on any basis. Hudson, in 1912, recognised that tumours arising in the stem of the optic nerve were all of the same nature, and he classified them as degenerative gliomatosis of the optic nerve. Verhoeff (1932), although regarding them as true gliomas, did not attempt to classify them on an embryological basis. He noticed that the tumours did not advance by direct spread, but by causing the pre-existing neuroglia in the vicinity to proliferate. The tumours are composed of neuroglial cells, which vary from adult astrocytes to elongated spindle-shaped cells taking on the character, more or less, of spongioblasts. There is generally a variable formation of neuroglial fibres, and the tumour, in parts at any rate, is superimposed upon the actual structure of the nerve. These tumour formations are generally classified as polar spongioblastomas, but Russell and Bland (1934) have subjected one specimen to tissue culture, and found that stellar astrocytes were grown, so that they consider that the tumour should be designated piloid astrocytoma. This observation indicates clearly the tendency of the cells in the tumour to differentiate along normal lines. These are all features well exemplified in the cases of gliomatosis cerebri, and it seems possible that tumours of the optic nerve may be primarily a blastomatous malformation, dependent upon some congenital developmental anomaly, and cases have been described in association with Von Recklinghausen's disease. On such a basis the great variety of the histological picture may be better understood. Glioma of the pons and optic thalamus also show many features similar to those found in gliomatosis cerebri. The cells in the tumours are round, oval, and elongated cells clearly neuroglial in origin, with a tendency to grow in a very diffuse manner between the essential nervous elements, with special condensations underneath the pia, and sometimes, especially in the thalamus, around nerve cells. Classification of these tumours has been much discussed, and it is possible that again they may be dependent upon some congenital abnormality of the neuroglia with a greater tendency in these cases for the blastomatous malformation to be lost in true tumour growth. In the second case of gliomatosis cerebri in this paper, a minute focus of true tumour growth having the characters of a spongioblastoma multiforme was found amidst the general cellular overgrowth. It is conceivable that cases might arise in which the picture was reversed, and large areas of tumour formation obscure the primary blastomatous malformation.

These suggestions with regard to the above-mentioned gliomas have been made because the patent similarities with the cases of gliomatosis cerebri indicated the possibility of a different angle of approach to their study. Further study of these tumours, however, and of the neuroglial system as a whole in such cases, may furnish information which will adequately explain their histogenesis, and in so doing throw further light on the cases of gliomatosis cerebri. A possible relationship also exists between the cases classified by Elvidge, Penfield and Cone (1937) as diffuse astrocytoma and gliomatosis cerebri because it seems inadequate to regard simply as a diffuse astrocytoma a pathological change which shows embryonic cells like spongioblasts differentiating into astrocytes, the retention of nerve cells in the midst of the tumour, and the accumulation of tumour cells around those nerve cells.

SUMMARY.

Three cases of diffuse cellular overgrowth of neuroglial cells throughout wide areas of the cerebral hemispheres have been described and correlated with other cases from the literature. The name gliomatosis cerebri has been considered most suitable for cases of this type, and they have been regarded pathologically as primarily blastomatous malformations arising upon a congenital developmental defect, although it is clearly recognized that it may be impossible to say where malformation ends and true tumour formation begins. Clinically, the cases were characterized by a long history of epilepsy, followed by mental symptoms, especially failure of memory and character changes and symptoms of increased intracranial pressure. Symptoms of focal disease in the brain were absent or late. The relation of the cases to certain localized tumour formations in the nervous system has been discussed.

This work was carried out during the tenure of the Pinsent Darwin Studentship in Mental Pathology.

I wish to thank the Physicians who have allowed me to publish their cases. My thanks are also due to Professor Pulvertaft for permission to take the photomicrographs; and to Dr. Denny Brown for photomicrographs 15 and 17. I also wish to thank Dr. Greenfield for his criticism and advice.

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LEGENDS FOR PLATES V, VI, VII.

Fig. 2. *Case 1.*—Camera lucida drawing from preparations stained by Hortega's silver carbonate method for astrocytes. (*a*) Examples of the cell types found in the thalamus. (*b*) Cellular layers of the cortex showing the varied size and shape of the new formed cells. Those round the nerve cells are astrocytes and spongioblasts. (*c*) Molecular layer of the cortex showing the marginal bundles of piloid fibres and bipolar cells, and also the predominance of astrocytes in the deeper parts of the layer.

Fig. 3.—*Case 1.*—Perivascular overgrowth displacing the myelinated fibres in the thalamus. Spielmeyer's myelin stain counterstained with carmine.

Fig. 4. *Case 1.*—Fibrillar bundles of cellular overgrowth along the cortical margin. Iron hæmatoxylin and van Gieson.

Fig. 5. *Case 1.*—Dense cellularity running along a blood-vessel into the cortex. The surrounding cortical infiltration is moderately severe. Nissl.

Fig. 6. *Case 1.*—Severe overgrowth in the cellular layers of the cortex, with distortion of the remaining nerve cells. Nissl.

Fig. 7. *Case 1.*—Dense subpial cellular overgrowth along both sides of a cerebral fissure. Iron hæmatoxylin and van Gieson.

Fig. 8. *Case 1.*—Subpial infiltration in the cerebellum. Iron hæmatoxylin and van Gieson.

Fig. 12. *Case 2.*—Severe cellular overgrowth in the cellular layers of the cortex. One or two nerve cells remain, and there is calcification in relation to a vessel. Iron hæmatoxylin and van Gieson.

Fig. 13. *Case 2.*—Same region as fig. 12. Bundles of neuroglial fibres running along small blood-vessels. The coarse neuroglial fibres in the background are only faintly stained. Anderson's victoria blue.

Fig. 14. *Case 2.*—Dense gliosis in the subcortical white matter. Anderson's victoria blue.

Fig. 15. *Case 2.*—Moderately severe cellular infiltration of the cortex showing clumping round nerve cells and the arrangement of the new formed cells in short chains. Iron hæmatoxylin and van Gieson.

Fig. 16. *Case 2.*—Focus of anaplastic tumour formation in the left frontal lobe. Davenport's stain.

Fig. 17. *Case 3.*—Severe cellular infiltration in the cortex showing residual nerve cells. Iron hæmatoxylin and van Gieson.

SUBACUTE DIFFUSE EPENDYMITIS.

BY R. M. STEWART.

It is possible to recognize three forms of ependymitis, the acute, the subacute, and the chronic. Of these the first named is a comparatively common condition, being in most cases either merely the extension of a purulent leptomeningitis to the ventricles of the brain, or, as in meningococcal meningitis, part of a septicæmia in which the organisms reach the ventriculo-subarachnoid system not by way of the meninges, but through the choroid plexus. In those instances in which the patients survive the acute phase of their illness this type of ependymitis, by closing the avenues of escape for the cerebrospinal fluid, may produce internal hydrocephalus as an end-result.

Chronic ependymitis is of an altogether different character. For example, the so-called granular ependymitis characteristic of parenchymatous syphilis owes its development more to a subependymal glial overgrowth than to an actual hyperplasia of the ependymal lining and its presence is but one indication of a widespread proliferative gliosis which spares no part of the nervous system.

On the other hand, subacute ependymitis differs from the other two forms in that it is capable of arising as an isolated and primary inflammation of the entire ventricular system, strictly limited to this system, with no concomitant inflammation in the subarachnoid space.

As in the case now reported the clinical features to which the condition gives rise may be puzzling and are often suggestive either of posterior fossa neoplasms or suprasellar tumours.

Case Report.

History.—E. H., aged 56, single, was admitted to Leavesden Hospital on December 5, 1933, in a condition of secondary dementia. She had been feebleminded all her life and from April, 1926, to December, 1933, was a patient in Bexley Hospital, the clinical history being one of depression, agitation, delusions of persecution and hallucinations of hearing.

State on Examination, December 5, 1933.—The patient was very obese. Height 4 ft. 10 in., weight 14 st. 9 lb. Her articulation, pupils and cranial nerves were normal, but her gait was feeble and unsteady and pain in the back was a prominent symptom.

Progress.—Three weeks after admission tremor of the right hand was noticed and pain was now complained of in the arms. In June, 1934, six months after admission, she had become even stouter, walking was more difficult and the tremor of the right hand more pronounced. Her urine was free from sugar and a sugar tolerance test gave the following readings:—

0 hr. = 125 mg. per 100 c.c.
½ hr. = 187 ,, ,, ,, ,,
1 hr. = 227 ,, ,, ,, ,,
1½ hrs. = 186 ,, ,, ,, ,,
2 hrs. = 173 ,, ,, ,, ,,

Serum calcium 10·7 mg. per 100 c.c. Serum phosphorus 4·6 mg. per 100 c.c. Blood-pressure 150/60.

Roentgenographic examination of the skull negative. Normal pupillary reactions continued to be obtained and the fundi showed no abnormality.

In December, 1934, twelve months after admission, the patient appeared to be in failing health ; the heart sounds were feeble, cyanosis was present and patches of pigmentation, first noticed in July, had become much more marked, especially in the axillæ, groins, and round the umbilicus. The patient was emotional, crying incessantly, salivating and dribbling. There was no pyrexia.

In January, 1935, the conjunctivæ and skin acquired an icteric tinge and for the first time involvement of the cranial nerves was detected. The pupils, equal in size, reacted sluggishly to light and on accommodation-convergence ; a left external strabismus and right-sided facial paresis were noted. The face was expressionless and this, coupled with tremor of the fingers of the cigarette rolling type, gave the patient an appearance somewhat suggestive of Parkinsonism. The lower limbs showed no tremor or rigidity and all deep reflexes were brisk. The patient was still able to leave her bed and sit in a chair for short periods.

In April, 1935, sixteen months after admission, remittent fever of a mild grade, which never exceeded 101° F. was recorded. The jaundice and cyanosis were more marked, the left border of the heart was displaced outwards and the patient had become considerably less obese, the reduction in weight amounting to 3 st. Vomiting occurred at infrequent intervals. Tremor of the fingers was still present and both upper limbs were somewhat rigid. The plantar reflexes were normal, the arm-jerks brisk, the knee and ankle jerks absent. Pain in the arms and shoulders was a prominent feature, and with increasing cyanosis and dyspnœa the patient became drowsy and gradually weaker. Several days before death small purpuric spots appeared on the abdomen and legs. Death occurred on May 26, eighteen months after the onset of symptoms.

Post-mortem examination.—An autopsy was held fourteen hours after death. The body was that of an extremely obese adult female, the distribution of fat affecting the shoulder girdles, upper limbs, breasts, abdomen, thighs, and buttocks. There was a noticeable degree of dark pigmentation of the breasts and groins. The fingers showed a slight degree of clubbing. The thyroid gland was normal, the lungs showed basal congestion and the heart considerable enlargement, weighing 360 grm. The left ventricle showed hypertrophy, the right ventricle dilatation. The coronary arteries showed a moderate degree of atheroma, but on the whole the myocardium was fairly healthy. On the mitral surface of each of the three aortic valve cusps there were numerous small vegetations of a red colour. These were not firmly attached and there was no ulceration of the valve segments. The remaining valves were healthy. The liver—1,055 grm.—showed a moderate degree of fatty infiltration; the spleen was moderately enlarged, soft and friable. The kidneys showed no gross changes. The lower end of the ileum, the cæcum and the first two feet of the ascending colon were gangrenous, owing to an embolic blockage of a branch of the superior mesenteric artery.

Nervous system.—The calvarium and dura mater were slightly thickened. The brain weighed 1,350 grm., and it was evident that a considerable degree of internal hydrocephalus was present. On removal of the brain the pituitary gland was seen to be markedly compressed. Except in the interpeduncular fossa and in the neighbourhood of the Sylvian fissures the pia-arachnoid was quite normal; in these situations the pia was slightly thickened but there was no evidence of exudate: at the base the arteries showed a moderate degree of atheroma. Some flattening of the fronto-parietal convolutions was present, otherwise they were of normal configuration. The cerebral hemispheres after ten days' immersion in formol saline were divided and weighed: right cerebral hemisphere, 485 grm.; left cerebral hemisphere 490 grm.; cerebellum and brain-stem 149 grm. The most obvious feature was the extreme degree of ventricular dilatation, more marked on the left side and affecting equally the body and horns of the lateral ventricle. The septum lucidum was thickened and the corpus callosum thinned and stretched. Both foramina of Monro were dilated and the 3rd ventricle markedly distended, its floor bulging downwards in a caudad direction. The 4th ventricle did not share in the dilatation (fig. 1). The cerebrospinal fluid which escaped from the ventricular system was clear and limpid.

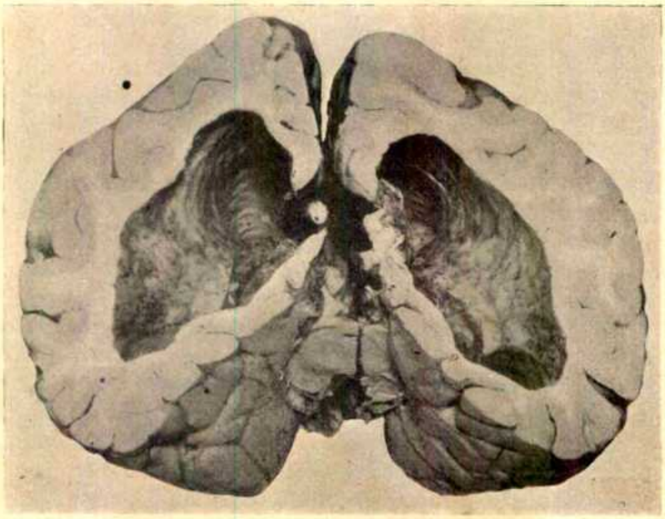

FIG. 1.—Vertical coronal section of cerebral hemispheres to show ependymitis of the greatly dilated anterior horns of the lateral ventricles. ⅝ actual size.

PLATE VIII.

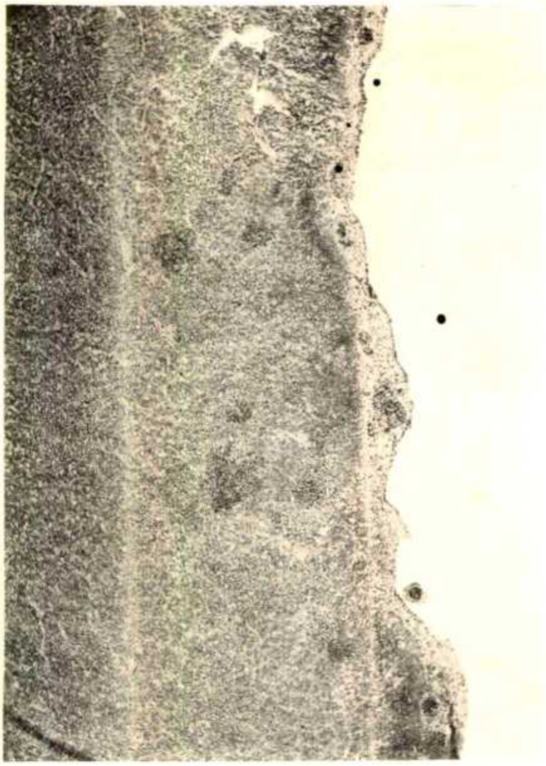

FIG. 2.

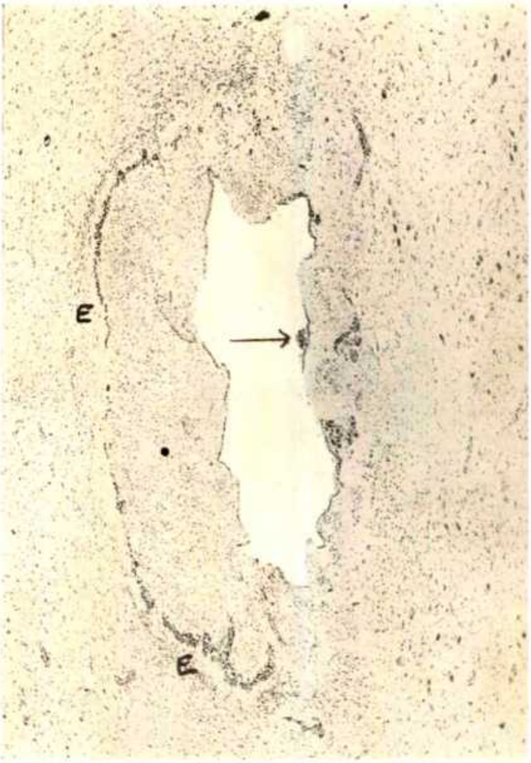

FIG. 3.

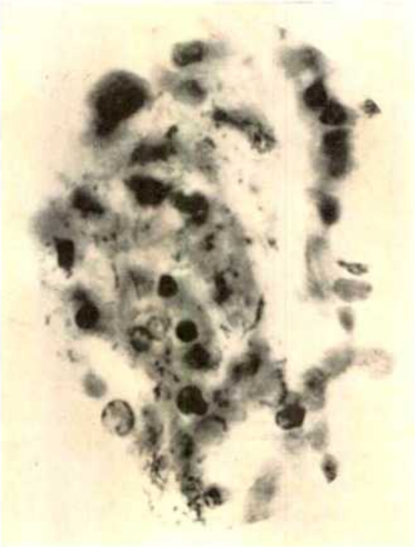

FIG. 4.

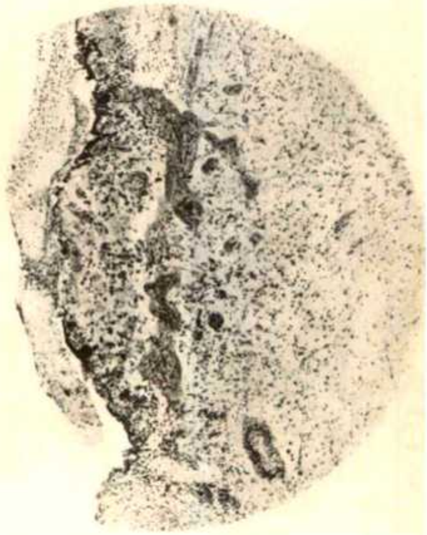

FIG. 5.

To illustrate paper by R. M. Stewart.

The ventricular walls presented a most unusual appearance. Instead of the smooth glistening surface the ependyma was rough, uneven and peppered all over with dark hæmorrhagic spots, many of the size of a pin's head. With a hand lens it could be seen that the ventricular lining had a decidedly granular appearance. These changes were most marked on the outer walls of the anterior horns, on the mesial walls of the occipital horns and on the walls of the 3rd ventricle. The inflammatory process also extended to the floor of the 4th ventricle where the ependymitis was so marked as to conceal the normal outlines of anatomical areas.

The choroid plexus did not appear flattened or bound down by inflammatory exudate.

At its commencement the aqueduct of Sylvius was slightly dilated but at its lower end it narrowed gradually until about 1 mm. above its termination it appeared to be almost completely occluded.

Microscopic appearances.—The pia-arachnoid investing the cerebral hemispheres showed no evidence of inflammation but some thickening and œdema were present in the neighbourhood of the Sylvian fissures.

In the cortical grey matter singularly few changes of an inflammatory character were present ; in particular there was no evidence of perivascular infiltration, and no pyæmic foci were found ; the glial components showed slight reaction. The cyto-architectonics were undisturbed although the larger nerve cells showed chromatolytic changes of a rather acute character. The " verödungsherde " characteristic of bacterial endocarditis were not found. The underlying white matter and the basal ganglia also participated in this relative freedom from inflammatory phenomena, but near the ventricular walls inflammatory changes were present in the brain substance and these became more pronounced as the free ependymal surface was approached. Many of the blood-vessels in this neighbourhood showed small-celled perivascular infiltration and nearly all contained masses of polymorphs in their interior. Organisms, however, could not be found either in or around the vessels.

Glial reaction was present both in the neighbourhood of these vessels and in the subependymal region. Numerous astrocytes, oligodendroglia and " gemastete " cells were present in the peri-ependymal region, and in the same locality small hæmorrhages occurred in large numbers (fig. 2).

On some parts of the ventricular wall the cells of the ependyma were intact and retained their cuboidal shape, in other situations they had entirely disappeared, or had proliferated and lay under a fibrinous exudate in which were lymphocytes, polymorphonuclear cells, fibroblasts and plasma cells, the latter in small numbers. Clumps and short chains of cocci, often forming solid masses, could be seen lying in the inflammatory exudate on the walls of the lateral ventricles and also in situations where there was little evidence of inflammation ; although they were present throughout the ventricular system nowhere else were they found in such large numbers.

The inflammatory changes described above were also very marked in the walls of the 3rd ventricle but the outer walls of the descending horns of the lateral ventricles were singularly free from evidence of inflammation though organisms could be seen lying on the free surface of the ependyma in this situation.

In the region of the aqueduct of Sylvius important changes were present. The ependymal cells had undergone proliferation but very irregularly, so that side by side with ependymal granule or hillock formation there were areas in which their arrangement was quite undisturbed. Towards its lower end the aqueduct was partially closed by a productive inflammatory process in the fibrous meshwork of which nests of ependymal cells could be discerned. Under a high power, chains and clumps of cocci could be seen lying in the midst of inflammatory cells but no organisms were found in the deeper layers of the peri-aqueductal grey matter. Complete closure of the iter had not occurred though its lumen was much encroached on and at one point separated up into several small canals (figs. 3 and 4).

Equally striking was the very marked degree of subependymal gliosis which became more pronounced at the lower end of the canal. On the floor of the 4th ventricle it formed a dense felt-like mat overlaid by proliferating ependymal and inflammatory cells lying among which were numerous organisms (fig. 5). In addition to the fibrous glia the peri-aqueductal grey matter contained swollen glial cells and nerve cells which exhibited acute degenerative changes. In this locality, too, some of the blood-vessels showed hyaline degeneration of their walls. Small hæmorrhages were also found in the subependymal region of both the pons and medulla. In the same localities endovascular leucocytic clumping was conspicuous but no organisms were found in the interior of vessels.

Many of the nerve cells of the pons were heavily pigmented.

The spinal cord showed a moderate glial increase of the astrocytic type but the vessels showed no perivascular infiltration. The central canal was closed. On the other hand, the investing pia-arachnoid was thickened and showed a pronounced inflammatory reaction, the condition being in fact a leptomeningitis of a rather acute character. For the most part the exudate consisted of polymorphs, lymphocytes and mononuclear phagocytes and a small amount of fibrin. Lying among the inflammatory cells were numerous Gram-positive cocci, often arranged in short chains.

The choroid plexus.—Both in the lateral and 4th ventricles the choroid plexus showed little evidence of inflammatory reaction, it being impossible to say that any marked degree of choroiditis existed. Some œdema and vascular dilatation was present but on the whole the tuft cells were singularly free from degenerative or inflammatory changes.

Discussion

In the absence of any widespread inflammatory reaction either in the cerebral cortex or of its membranes it is evident that we are here dealing with an example of the relatively uncommon form of ependymitis for which the term primary is justifiably employed. In this type the inflammatory process is strictly limited to the ependymal lining of the intraventricular system of the brain and the symptoms to which it gives rise are largely those of an obstructive hydrocephalus secondary to closure of the ventricular foramina. With regard to the ætiology of these cases little is known.

In a case of acute ependymitis to which the patient succumbed within forty-eight hours, Coutts (1903) isolated streptococci from the ventricular fluid, but no infection was found in the other organs. In a closely analogous case in which Fisher (1903) reported the co-existence of acute ependymitis with lobar pneumonia, Friedländer's diplobacillus was present in the ventricular fluid as well as in the lung tissue. But in the subacute type direct evidence of infection is almost always lacking and for an explanation of the strict limitation of the inflammatory process to the ventricular system it is necessary to assume the presence of an abnormal permeability of the blood-brain barrier which permits bacteria or toxins to pass from the circulation through the choroid plexus to the cerebrospinal fluid. In recent years several striking examples of subacute ependymitis have been reported. In the case reported by Globus and Strauss (1928) the illness, which was marked by remissions and exacerbations, lasted ten months ; symptoms suggestive of tumour of the 3rd ventricle were observed, and ventriculography revealed an obstruction of both foramina of Monro. At the autopsy a subacute inflammatory process involving the entire ventricular system was found. In the 3rd ventricle the ependyma and subependyma had separated from the wall of the cavity to form a pseudo-cyst which partly blocked the aqueduct of Sylvius. Careful search failed to reveal any evidence of inflammatory reaction in the choroid plexus nor were the mild degenerative and inflammatory changes seen in the adjacent brain tissue anything more than a reaction to a contiguous inflammatory process. In the widespread ependymitis there were present all gradations from the mildly acute purulent in the lateral ventricle to the chronic granular ependymitis in the aqueduct and 4th ventricle.

On the basis of these findings the authors suggested that at least some instances of chronic granular ependymitis have their beginnings in mild and slowly progressive acute forms.

Other accounts of this condition have been recorded by Merle (1910), Tillgren, Spiller (1902), Cushing (1903), and Arnold, Jr. (1934).

In the case of Arnold the similarity of the pathological findings to those described by Globus and Strauss was striking. The patient's illness lasted little more than two months and the outstanding symptoms were those of mental deterioration and headache. The neurological signs were bilateral and of little localizing value. Ventriculography showed symmetrical dilatation of both lateral ventricles, the other ventricles being of normal size. No organisms were found in the cerebrospinal fluid withdrawn from the lateral ventricles. The pathological changes consisted of obstruction of the foramina of Monro by a subacute inflammatory process ; there were present a marked glial reaction, destruction of the ependymal lining, swelling and hyperplasia of the choroid plexus, a marked perivascular lymphocytic reaction involving the subependymal tissues of the entire ventricular system and the presence in many places of isolated ependymal granulations. There was no evidence of visceral syphilis and bacteria were not found. Though not normal the cerebral aqueduct was not obstructed.

It will be observed that in both of these two cases closure of the foramina of Monro played a major part in determining distension of the lateral ventricles, but obstruction of the Sylvian aqueduct by itself must be reckoned almost as common as a cause of internal hydrocephalus; in such cases the 3rd ventricle will naturally participate in the distension, while the 4th ventricle retains its normal size and shape.

Of this type of occlusion there have been numerous reports but it is noteworthy that few, if any, of these can be regarded as instances of subacute ependymitis, peri-aqueductal tumours and simple hyperplasia being commoner causes of obstruction. Usually, too, the changes are of a chronic character, the brunt of the damage falling on the peri-aqueductal tissue which becomes the seat of a fibrous glial proliferation with but slight involvement of the overlying ependyma. Evidence of inflammation is, indeed, often conspicuous by its absence, and perhaps for this reason the view has been advanced that not a few of the proliferative cases are of developmental origin. It has been suggested by Spiller (1916) that the process of aqueductal narrowing which takes place late in fœtal life may proceed beyond the normal limits with a resultant hydrocephalus of the obstructive type at some period of postnatal life. According to this hypothesis the process is somewhat analogous to that which may occur under supposedly normal conditions around the central canal of the cord. But, as Stookey and Scarff point out, anatomical considerations lend no support for this analogy for the mechanism operative in closure of the spinal canal is different from that for the Sylvian aqueduct. In the former, simple fusion of the neural groove is followed by an obliterative process which spares only the most ventral part of the primitive central canal, whereas, in the aqueduct of Sylvius the primitive central canal is not obliterated, but merely undergoes modifications of shape and size owing to the encroachment on it of surrounding anatomical structures. The hypothesis of a developmental origin has also been contested by Dandy (1920) who postulates the intervention of some toxic, inflammatory or traumatic process occurring before or after birth and which, by injuring the aqueductal lining, brings about a secondary glial overgrowth and finally stenosis.

Cases of occlusion of the aqueduct by a diffuse inflammatory process involving almost the whole ventricular lining have been reported by

Sheldon, Parker, Kernohan (1930) and by Orton (1931). The appearances in the two cases recorded by Sheldon and his co-workers were dissimilar. In the first the condition was visible to the naked eye as a thick, gelatinous exudate covering the surface of the lateral and 3rd ventricles ; on microscopic examination this was seen to consist of masses of chronic inflammatory cells. In the second case there was diffuse granular proliferation of the subependymal tissues and instead of a smooth exudate there were visible innumerable small granules, constituting the so-called granular ependymitis. In neither case was it possible to ascertain how the infection was acquired nor by what pathways it had entered the ventricular system. It must, however, be noted that both these cases belonged to the chronic rather than to the subacute type, the duration of the illness being two and four years respectively. But even in the subacute type where pericanalicular gliosis is less conspicuous than the ependymal involvement and where there is often clear indication of an inflammatory origin in the adjacent perivascular spaces, the actual cause usually remains obscure.

From this aspect the case now reported is exceptional for not only was there abundant evidence of inflammation in the subependymal tissues but no difficulty was experienced in demonstrating the presence of large numbers of micrococci in the fibrinous exudate on the walls of the ventricular cavity. Though unfortunately the identification of these organisms by culture was not attempted it can hardly be doubted that they were derived from the bacterial endocarditis to which the patient succumbed. Concerning this disease, it may be recalled that it usually presents a fairly definite symptomatology. The insidious onset, the variable fever, the brownish pigmentation of the skin, dyspnœa, progressive cardiac failure, clubbing of the fingers and embolic phenomena form a composite clinical picture which can hardly escape recognition. It was reproduced with great fidelity in this patient though whether it was caused by the *Streptococcus viridans*—the organism most frequently found in subacute endocarditis — must remain undecided. The presence of organisms flourishing in enormous numbers on the endocardial surface of the heart with little or no response from phagocytic cells is a striking peculiarity of bacterial endocarditis and in this case was illustrated by masses of organisms lying on the ventricular surface with no accompanying invasion by polymorphs.

Concerning the mode of infection of the ventricular system it is not possible to speak with any degree of certainty. It seems obvious, however, that the cerebrospinal fluid in the ventricles was not infected from without, that is to say from the meninges, since no organisms and no evidence of inflammation were present in the pia-arachnoid, save in one situation —the upper cervical region of the cord—and in this area the acuteness of the inflammatory process spoke in favour of a terminal stage of meningitis attributable to the escape of organisms through the roof of the 4th ventricle.

In a disease such as subacute endocarditis in which organisms are widely disseminated through the blood-stream, infection of the brain tissues is to be expected, and has, indeed, been frequently reported, notably by Kimmelstiel, who found aneurysms, vascular thrombosis, ischæmic foci and multiple inflammatory areas in the cerebrum. Consequently the likelihood of infection of the cerebrospinal fluid from the blood-stream must be entertained. In the case under discussion no changes of the widespread character described by Kimmelstiel were found, evidence of inflammatory reaction being limited to the neighbourhood of the ventricular walls. No thrombosed vessels or ischæmic foci were seen and the possibility of infection from this region is purely presumptive.

Certain writers have claimed that organisms can reach the ventriculo-subarachnoid system not by way of the meninges but through the choroid plexus and obviously the presence in this situation of a metastatic focus would afford a direct route for invasion of the cerebrospinal fluid. In one of their two cases of diffuse inflammatory ependymitis, Sheldon and his co-workers found in the choroid plexus of the lateral and 3rd ventricles lymphocytes, polymorphs and small thrombosed vessels so that notwithstanding the negative character of the histological appearances in the case under discussion the possibility of a mechanism of this sort must be given serious consideration.

In this case the degree of proliferative gliosis which accompanied the ependymitis was so marked, especially in the pons and medulla as to raise the question of whether the gliosis may not have preceded the involvement of the ependyma, the organismal invasion being thus a secondary phenomenon attacking an already diseased system and, perhaps, limited in time to the last few weeks of the patient's illness.

As already mentioned, alternative hypotheses have been advanced in explanation of aqueductal stenosis of long standing; of these the first postulates an involutional or developmental hyperplasia of the subependymal glia, the second holds that the proliferative changes in the glia are secondary to some previous inflammatory process that has resolved, leaving no vestige of the original infection which brought them into being. For the first view there is something to be said when the patient succumbs at a comparatively early age, as in the cases recorded by Spiller

(1902) and Dijkstra (1930) or when, as in Orton's case (1931), the patient has a hydrocephalic type of cranium indicating that imperfect drainage of ventricular cerebrospinal fluid must have been present at an age when growth of bones of the skull was still active, but in the case now reported the patient showed no enlargement of the head and since she had attained her fifty-sixth year, a developmental gliosis commencing at so late a period of life would be most unlikely. On the other hand, the duration of her illness and the whole clinical history were quite compatible with the presence of an infective ependymitis pursuing a comparatively slow and insidious course and since evidence was not lacking of reactive phenomena of fairly long standing beneath the ependyma it may legitimately be concluded that the lowness of the virulence which confers on bacterial endocarditis lenta its subacute character was in this case responsible for the changes produced in the ventricular walls and in the aqueduct of Sylvius.

Finally, it may be remarked that, as in this case, complete closure of the aqueduct of Sylvius is not necessary for the establishment of a progressive ventricular dilatation. This channel is normally so minute that even a moderate encroachment on its lumen seems to be sufficient to determine an obstructive hydrocephalus.

From the diagnostic standpoint it was unfortunate that efforts to obtain a sample of cerebrospinal fluid were unsuccessful, for the presence of organisms in the fluid would have afforded a clue to the nature of the condition. Without this diagnostic aid the patient's symptoms—mental deterioration, change of personality, headache, vomiting, muscular rigidity and tremor, cutaneous pigmentation and increasing obesity—were misleading and were indeed interpreted as evidence of an intracranial neoplasm with probable involvement of the pituitary body. This simulation of intracranial tumour in subacute ependymitis has been noted by a number of other writers and it is clear from accounts in the literature that even when all diagnostic aids, including ventriculography, are employed, occasionally the actual cause of the internal hydrocephalus can only be determined by an exploratory operation.

SUMMARY.

A feebleminded woman, aged 56, succumbed to bacterial endocarditis of eighteen months' duration. Examination of the nervous system showed the presence of a subacute ependymitis of the lateral 3rd and 4th ventricles ; associated with this there was a partial stenosis of the aqueduct of Sylvius which had produced a marked degree of internal hydrocephalus. Inflammatory changes were limited to the ependymal and subependymal

regions of the brain and except for the presence of a leptomeningitis in the upper cervical region of the cord, the pia-arachnoid was free from evidence of inflammation. Large numbers of micro-organisms were present among inflammatory cells lying on the surface of the ependymal lining of the ventricles. A marked proliferation of the subependymal glia accompanied these changes.

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LEGENDS FOR PLATE VIII.

Fig. 2.—Wall of 3rd ventricle. Note the irregular ependymal surface and the presence of free hæmorrhages in the subependymal tissue. Mallory's stain. × 50.

Fig. 3.—Lower end of aqueduct of Sylvius showing partial stenosis. Note submerged ependymal cells E. Arrow points to a clump of polymorphs containing many cocci. Cresyl violet stain. × 34.

Fig. 4.—High-power view of the clump of polymorphs indicated in fig. 3. The organisms are streptococci arranged in short chains. × 600.

Fig. 5.—Floor of 4th ventricle showing intense gliosis. The ependymal cells are still present. Cresyl violet. × 38.

THE CENTRAL PATHWAY IN MAN OF THE VASOMOTOR RESPONSE TO PAIN.[1]

BY D. G. MARQUIS AND D. J. WILLIAMS.

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INTRODUCTION.

LITTLE is known of the intramedullary pathways governing the activity of the sympathetic nervous system in man. Clinical and experimental observation have given rise to speculation concerning "centres" in the cerebral cortex, the hypothalamus or the medulla, and to conjecture as to the tracts below this level. The issues cannot be completely settled by animal experimentation, for the results are frequently at variance from one species to another, and in some points are in clear disagreement with the results obtained from the study of man.

Since the peripheral sensory nerves are known to be the afferents for sympathetic response as well as for somatic sensation, it may be possible to study the relation of the intramedullary pathways involved in sensory perception to those used by the sympathetic response. At those points in the central nervous system where the two pathways are identical, any pathological lesion resulting in sensory changes should likewise result in corresponding changes in the sympathetic responses to the stimuli. Conversely, where the two pathways are not identical, there should be a dissociation of the sensory changes and the sympathetic responses.

Accordingly, a series of patients with lesions of the nervous system at various levels from peripheral nerve to cortex were selected for study. The patients all presented marked sensory changes, either a decrease or an increase in the intensity of the subjective appreciation of peripheral stimulation. The sympathetic response selected for measurement was the vasoconstrictor response recorded with a finger plethysmograph.

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[1] Work undertaken in the Research Unit, The National Hospital, Queen Square, London, under the tenure by Dr. Marquis of a Rockefeller Travelling Fellowship, and by Dr. Williams of a Halley Stewart Research Fellowship.

We wish to thank those members of the Staff of the National Hospital, Queen Square, who allowed us to study their patients in this investigation, and those normal subjects who served as controls. We wish also to thank Dr. J. Doupe for his help in some of the experimental procedures, and Dr. Carmichael for his valuable advice and criticism.

METHOD.

The technique used in recording vasomotor responses has been described in detail elsewhere (Bolton, Carmichael and Stürup, 1936). A small glass plethysmograph was placed on a finger or toe and sealed with zinc oxide paste. The plethysmograph was connected by pressure tubing to a tambour on which was mounted a mirror which reflected a beam of light to the slit of a continuous film camera. The optical magnification provided a recorded excursion of approximately 1 mm. per 10 c.mm. of finger volume change. (*see* fig. 1).

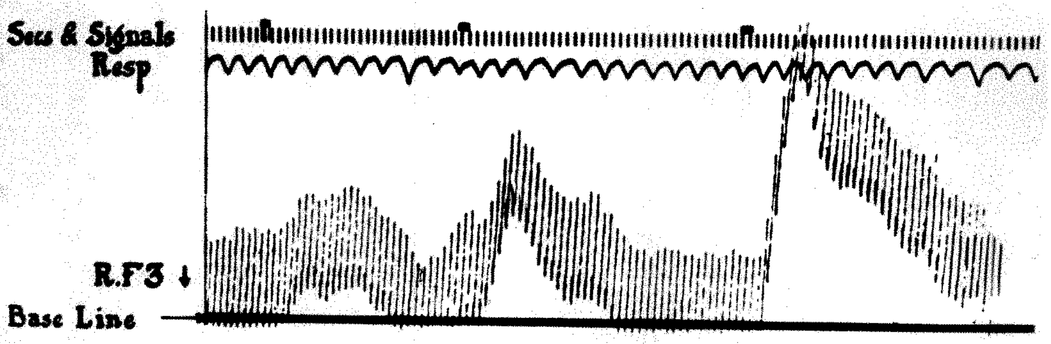


FIG. 1.—The vasoconstrictor responses to equal stimuli on skin areas of differing sensitivity. The volume of the right middle finger and the respiratory phases of Case 1 are recorded. The record reads from left to right, the arrow points in the direction of an increase in finger volume, and time is recorded in seconds. At the first signal a single pin-prick was made in the hypalgesic area, causing a deflection of 5 mm., at the second a similar prick on the normal skin caused 15 mm. deflection, and at the third the same stimulus on the hyperalgesic area caused a deflection of 33 mm. of the recording beam of light.

The sensory stimuli employed to evoke the vasomotor responses were carefully calibrated and standardized to ensure the objective equality of stimuli applied to normal and affected regions of the body. The pin-prick stimulus was delivered by means of a modified Head algesiometer, with which the intensity could be varied by adding or removing weights. After preliminary experiment two intensities were selected for subsequent work. These have been designated as " weak " and " strong " pin-prick. The former was normally perceived as sharp but not unpleasant; the latter was definitely painful and when applied without warning was apt to provoke retraction of the part stimulated.

Pressure stimulation was applied with a calibrated spring instrument which indicated pressures of 1 to 10 kg. The contact surface was a rounded bakelite button 1 cm. in diameter.

Temperature stimuli were obtained by the application of flat-bottomed copper calorimeters, 5 cm. in diameter, which were filled with water of measured temperature. Stimuli designated as " hot " were between 45° and 50° C.; the " cold " stimuli were between 0° and 10° C.

Stimuli were applied to the patient in a predetermined random order at various points on the body in order to avoid any marked adaptation effects. Sufficient time elapsd between stimuli for the return to the basic dilated state. Note was made of any verbal or expressive indications of the painfulness of the stimuli, and at one or more times during the experiment the patient was asked to compare systematically the sensory qualities of the stimuli on the normal and affected parts of the body.

Since previous experiments in this laboratory have shown that the response to sensory stimulation is invariably in the direction of vasoconstriction, records were taken only when the skin vessels were maximally dilated. This provided a constant background condition for all cases, upon which the vasoconstrictor response was clear and definite. The dilatation was brought about in most instances by immersion of both legs in a water bath at about 43° C.

In some cases plethysmographic records were obtained from a finger of both the right and left hands, but in no instance was any constant difference between the magnitude of the responses on the two sides noted. The results, therefore, are reported for one digit only. This was usually the one on the unaffected side of the body, since the record was less disturbed by tremors or involuntary movements.

Simultaneous photographic records of the respiratory movements of the thorax were made in order to identify and eliminate from consideration those vasoconstrictor responses which follow deep inspiration.

Five normal young post-graduate students and twenty-three patients with focal lesions of the nervous system involving sensory pathways were examined. The abnormal patients were chosen with predetermined criteria in view. Their lesions were clinically well localized and in four were verified at operation. They had definite subjective sensory changes, were co-operative, and had normally responsive peripheral vascular beds.

Eight of the twenty-three patients failed to meet all of these criteria and were therefore discarded from the experimental series. In order adequately to compare the results obtained in patients with a "thalamic syndrome" an attempt was made to obtain some subjects with hyperalgesia as well as those with hypalgesia.

OBSERVATIONS.

To evaluate the results obtained from the patients with various lesions of the nervous system it was necessary to demonstrate in normal subjects that stimuli on the right and left sides of the body were equally effective in eliciting vasoconstrictor responses. Table I presents a summary of the data obtained from studies of the normal control group with various types of stimulation.

TABLE I.

Comparison of the vasoconstrictor responses in normal subjects to stimuli on the two sides of the body. Each value represents the mean of from 10 to 20 responses, expressed in millimetres of deflection. The columns headed "*t*" and "*P*" represent the statistical significance of the difference as explained in the text.

Subject	Stimulus	Right	Left	Difference	*t*	*P*
1	Strong PP *	14·9	15·0	0·1	0·035	0·9
	Cold	23·0	24·1	1·1	0·196	0·8
2	Cold	36·7	37·7	1·0	0·157	0·8
3	Strong PP	27·2	32·0	4·8	0·869	0·3
	Cold	40·3	43·9	3·6	0·526	0·6
4	Strong PP	14·9	14·2	0·7	0·215	0·8
5	Strong PP	32·6	30·4	2·2	0·325	0·7
	Cold	22·8	21·4	1·4	0·269	0·7

* Pin-prick.

Although the variability of vasoconstrictor responses was too great to permit comparison of single measurements, the average values for ten or more stimuli showed a striking correspondence between the two sides of the body. Consequently, all values reported in this study are means of from ten to twenty individual measurements.

The statistical significance of the differences between means was computed by Fisher's (1932) method for small samples. The ratio of the differences to the estimated standard error of that difference is called *t*, and from appropriate tables the probability (*P*) of the observed difference arising by chance is determined. When *P* is less than 0·02 (which signifies that the difference in question might be expected to occur fewer than twice in 100 samples drawn at random from a homogeneous population) the difference may be regarded as significant. It will be seen in Table I that none of the differences is large enough to be considered as anything but chance differences. It was also apparent that there were large differences between individuals in the magnitude of the responses to similar stimuli but since the problem of this study demands comparisons of one region of the body with another in the same person, the factor of individual differences does not enter into the results.

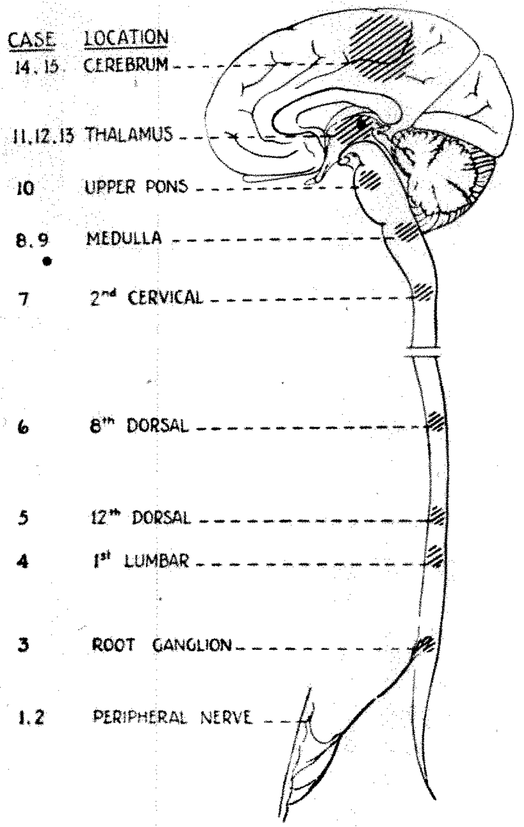
Preliminary investigation also demonstrated that there was a correspondence in normal subjects between the size of the vasoconstrictor response and the objective intensity of the stimulus. With increased severity of stimulation, and therefore greater subjective sensory intensity, the objective vasoconstrictor response was also increased. This may be illustrated by reference to Cases 3, 4, 12 and 15, with whom different intensities of pin-prick were employed. The results presented in Tables III and IV show that when the stimulus to either the normal or the abnormal area was increased, there was a corresponding increase in the mean vasoconstrictor response. Quantitative confirmation of this relationship has been obtained recently by Hovland and Riesen (1938), who recorded the vasoconstrictor responses to four intensities of electric shock, presented in random balanced order to eight normal subjects (Table II).

TABLE II.

Magnitude of vasoconstrictor responses in relation to intensity of electrical stimulation. Each value is the mean of about 12 responses in each of 8 normal subjects. The stimuli ranged by approximately equal steps from a very mild shock (1) to a moderately intense shock (4). Quoted by permission from unpublished data of C. I. Hovland and A. H. Riesen.

Strength of shock	Vasoconstrictor response (mm.)
1	11·3
2	16·5
3	19·7
4	24·4

The fifteen patients with diminished or exaggerated sensitivity to somatic stimulation have been considered in two groups. One group is composed of ten patients whose sensory disorder was due to involvement of the sensory pathway at some point below the level of the thalamus. The other group contains five patients with lesions at a thalamic or cerebral level giving rise to sensory changes. The former group contains two patients with involvement of the peripheral sensory pathway, one with dorsal root involvement, four with lesions of the spinal cord and three with lesions in the medulla or pons (fig. 2). Brief summaries of the clinical findings of the cases relevant to the diagnosis and to the nature of the subjective sensory changes and the objective vasomotor response to various stimuli follow. A detailed summary of the experimental results is presented in Table III.



POSITION OF THE LESIONS IN THE SENSORY TRACT

FIG. 2.

Group I.—Cases with a lesion of the sensory tract below the level of the thalamus.

Case 1.—Areas of hypo- and hyperæsthesia due to involvement of a peripheral nerve in scar tissue.

S. S., a male aged 51, was admitted under Dr. E. A. Carmichael on February 5, 1936. There was a painful scar in an amputation stump of the right thigh. There was no other abnormality of the nervous system. Sensation on the day of the experiment was as follows: Moderate pin-prick was appreciated on the hypæsthetic area as a dull touch, unassociated with pain. With stronger stimulation pain was appreciated. At no point was there absolute anæsthesia, but the patient preferred being pricked there to the normal part. Along the posterior edge of the scar there were several minute areas of hyperalgesia where pin-prick was felt as an unpleasant shock-like sensation, unlike the ordinary sharpness of a pin. There was no radiation of the sensation. It was more unpleasant than pricking on the normal areas.

TABLE III.

Comparison of the vasoconstrictor responses in the first group of patients to stimuli on the normal and affected regions of the body. The symbols are the same as in Table I.

Case	Level of lesion	Direction of sensory change	Stimulus	Normal region	Affected region	Difference	t	P
1	Peripheral	Hyperæsthesia	Strong PP	20·1	36·0	+ 15·9	3·06	0·01
		Hypæsthesia	Strong PP	20·1	15·1	− 5·0	1·01	0·3
2a	Peripheral	Hyperæsthesia	Strong PP	7·9	17·9	+ 10·0	3·20	0·01
			Cold	7·4	16·0	+ 8·6	2·68	0·02
			Pressure	2·7	16·5	+ 13·8	6·43	0·01
2b	Dorsal 8	Analgesia	Strong PP	9·1	2·2	− 6·9	1·94	0·07
			Cold	12·3	1·2	− 11·1	2·50	0·03
3	Dorsal 5	Hyperæsthesia	Weak PP	5·0	9·8	+ 4·8	1·58	0·1
			Strong PP	7·7	15·3	+ 7·6	2·01	0·06
			Pressure	6·7	14·3	+ 7·6	1·66	0·1
			Cold	2·3	12·3	+ 10·0	3·86	0·01
4	Lumbar 1	Hyperæsthesia	Weak PP	1·0	2·2	+ 1·2	1·48	0·1
			Strong PP	2·0	9·1	+ 7·1	3·96	0·01
			Cold	2·3	12·9	+ 10·6	6·81	0·01
			Hot	1·7	4·5	+ 2·8	2·13	0·03
5	Dorsal 8	Hypæsthesia	Strong PP	8·7	1·4	− 6·3	3·39	0·01
			Cold	17·9	2·5	− 15·4	6·70	0·01
6	Dorsal 4–8	Hyperæsthesia	Strong PP	5·9	20·9	+ 15·0	3·52	0·01
			Cold	7·0	27·2	+ 20·2	4·41	0·01
7	Cervical 2	Hypæsthesia	Cold	12·8	3·3	− 9·5	3·46	0·01
8	Medulla	Hypæsthesia	Strong PP	6·8	2·6	− 4·2	2·30	0·03
			Cold	2·5	2·3	− 0·2	0·10	0·9
9	Medulla	Hypæsthesia	Strong PP	9·7	6·0	− 3·7	1·27	0·2
			Cold	7·6	4·1	− 3·5	1·59	0·1
10	Pons	Hypæsthesia	Strong PP	11·9	3·7	− 8·2	3·03	0·01
			Cold	8·6	4·9	− 3·7	1·03	0·03

The vasomotor responses to pin-prick on the normal skin caused an average deflection of 20 mm. on the hypæsthetic area of 15 mm., and on the hyperæsthetic area of 36 mm.

Case 2.—(a) Hyperæsthesia due to involvement of peripheral nerve in scar tissue; (b) Analgesia below D.8 following subsequent chordotomy.

W. C., a male admitted under Dr. E. A. Carmichael in June, 1936, had extreme hyperæsthesia with spontaneous pain in an amputation stump of the right leg. Following a spino-thalamic section at the 8th dorsal segment there was analgesia below this level, with complete relief of his symptoms. Sensory examination before operation was as follows: In the distal third of the stump there was an area of hyperæsthesia where light touch had a rasping quality, "like sandpaper," deep pressure could not be tolerated at all, and pin-pricks caused violent withdrawals and were described as "like electric shocks." Cold produced a similar emotional over-response. Accurate descriptions of the sensations could not be obtained because of the subject's deafness and limited intellect. It was evident from comparison of the response to stimulation in other areas, however, that the hyperæsthesia was profound.

After operation there was analgesia to pin-prick, heat and cold below the 8th dorsal segment on the right. Pin-pricks were felt as dull tapping, but on extremely violent pinching with forceps a sensation of unpleasantness could be felt. Ice was described as a pleasant warmth below the level. There was a normal response to noxious stimuli elsewhere.

Before operation the vasoconstrictor responses to pin-prick and ice in the hyperæsthetic areas were over twice as great as on the normal side, while the response to pressure was six times as great. After operation the responses to pin-prick on the normal side were four times as great and to ice were ten times as great as from the analgesic area.

Case 3.—Post-herpetic hyperæsthesia.

W. H., a male, was an outpatient under Dr. J. P. Martin on February 2, 1936. In the hyperæsthetic area, which had resulted from herpes zoster of the right 5th dorsal segment, pin-prick was sharper and more painful, cold was colder, and pressure had a lower threshold and was more painful than elsewhere.

The vasoconstrictor responses to weak and strong pin-prick, pressure and cold on the affected area were increased from two to sixfold.

Case 4.—Hyperæsthesia due to a spinal cord lesion.

S. T., a male aged 27, was admitted under Dr. Grainger Stewart on January 25, 1936. There was a progressive paraplegia with flexor spasms in both legs and a sensory level at the first lumbar segment. Posterior column sensation was almost completely spared. There was increased sensitivity to pain and thermal stimulation. To pin-prick there was overaction above a raised threshold, the sensation of sharpness being lacking with moderate stimulation and a more painful component being present on stronger stimulation.

Moderate changes in temperature were normally appreciated, but there was marked overaction to extremes of temperature. Cold first felt burning hot and later felt cold, with a sharp pricking component. Heat was felt as normal below 50° C., but above this it was painfully hot and felt sharp. There was also a prolonged after-sensation. Pressure pain did not appear to be affected.

There was a significant increase in the vasoconstrictor response to graded painful and thermal stimulation below the level. Light pin-prick on the normal and abnormal areas—below the threshold—caused closely similar responses, while strong stimulation to the abnormal area caused five times the response that was produced from the normal area. Ice caused six times the response from the abnormal area, while heat gave twice the normal response.

Case 5.—Hypæsthesia due to lesions of the spinal cord at C.3 on the right, and D.8 on the left.

W. O., a male aged 45, was admitted under Dr. E. A. Carmichael on May 20, 1936. There was marked diminution to pain and thermal sensation on the left side of the neck, with wasting of the left shoulder muscles. There was also spastic paraplegia with diminution in posterior column sensation in the legs and in lateral column sensation below the 9th thoracic segment on the right. The average vasoconstrictor response to pin-prick on the normal skin surface was six times as great, and to ice was seven times as great as on the hypalgesic areas on the right.

Case 6.—Hyperæsthesia following spinal cord injury.

H. B., a male aged 36, was admitted under the late Dr. James Collier on September 25, 1934. Following an accident the patient had spasticity and weakness of the left arm and leg, with hyperæsthesia to all forms of sensation below the 4th dorsal segment on the left, and the 8th dorsal segment on the right. It was much more marked on the right side, and was most severe distally. Details of the sensory changes at the time of the experiment were as follows: Pin-prick was sharper, more sore, and hurt more over a greater area than normal. It radiated for a few inches from the point of stimulation. Moderate cold was described as stinging, scalding, and " like ice." Heat was not appreciated as heat, but hurt and had a stinging quality in it. Light touch was described as stinging ; it had an unpleasant tickle and felt stronger. Other forms of posterior column sensation were much diminished in the legs, the left being the more affected. The vasoconstrictor responses to pin-prick and to ice on the hyperalgesic area were increased nearly fourfold compared with the responses from the normal area.

Case 7.—Hypæsthesia due to spinal cord tumour.

D. B., a female admitted under Dr. C. P. Symonds, had an extra-medullary neoplasm causing damage to the spinal cord at the second cervical segment, with resulting hypæsthesia below this level. There was marked hypalgesia on the left.

The vasoconstrictor response to cold stimuli applied to the normal and abnormal areas was investigated. From the hypalgesic area it was diminished fourfold.

Case 8.—Hypæsthesia due to a lesion of the medulla.

H. H., a female aged 39, was admitted under the late Dr. S. A. K. Wilson on July 27, 1936, with the syndrome of thrombosis of the right posterior inferior cerebellar artery. There was diminution in pain sensation over the first division of the right trigeminal nerve, with diminution in pain and temperature sensation on the left side of the body which was most marked peripherally. In the left leg pin-prick was appreciated as a blunt and rather unpleasant sensation. Cold was felt as cold, but it was not at all unpleasant. It approximated more to touch than to thermal sensation. Similarly heat was not appreciated in its normal intensity. Posterior column sensation was normal.

The vasomotor response to cold was equal on the normal and abnormal areas, but that in response to pin-prick was nearly three times as small from stimulation in the hypalgesic area as in the normal area.

Case 9.—Hypalgesia due to a medullary lesion.

A. T., a male aged 58, was admitted under Dr. F. M. R. Walshe on July 7, 1936. There was diminution to all forms of sensation over the area of distribution of the right trigeminal nerve, with involvement of pain and thermal sensation on the contralateral side of the body as a result of thrombosis of the right posterior inferior cerebellar artery. The sensory changes at the time of the experiment was as follows: Moderately firm pin-pricks were felt as vague pressure, but hard pricks caused a pain like an electric shock. The threshold for this sensation was higher than that for pain on the left side of the body. Cold was felt as a warm sensation, but lower temperatures evoked an unpleasant tingling sensation in addition. Cortical forms of sensation were normal.

On the affected side strong pin-pricks caused a vasoconstrictor response of three-quarters of the normal, and ice of about half the normal.

Case 10.—Hypalgesia due to a tumour of the pons.

L. S., a female, admitted under Dr. E. A. Carmichael on August 19, 1934, was found at operation to have a cystic glioma of the posterior part of the upper third of the pons, extending into the 4th ventricle. The clinical signs corresponded to a lesion at this level. There was relative analgesia on the left side of the face, and absolute analgesia of the right side of the body. To pin-prick there was a numb sensation with an element of unpleasantness, and ice felt like "something smooth," but was not interpreted as cold. Other forms of sensation were unimpaired.

The average vasoconstrictor response to pin-prick applied to the normal side of the body was three times as great as that resulting from stimulation of the analgesic side, while the response to cold on the normal side was nearly twice as great.

The data for the patients in this first group is summarized in Table III. It will be seen that vasoconstrictor responses closely paralleled in magnitude the subjective intensity of the sensation. In cases with diminished sensitivity the vasoconstriction elicited by stimuli applied to the affected region was smaller than normal, and in cases with exaggerated sensitivity the vasoconstriction was larger than normal. In every instance the difference between the mean values for the affected and normal regions of the body is in the direction corresponding to the sensory change, and in more than half of the twenty-six comparisons the difference is statistically reliable (i.e. there are fewer than two chances in one hundred that the observed difference is due to chance).

Case 2 provides further definite evidence that the afferent spinal pathway for the vasoconstrictor response is identical with that for conscious perception of pain. The exaggerated sensitivity to stimuli in the region of the amputation scar was accompanied by a greatly increased vasoconstrictor response. Following the cordotomy there was complete analgesia on the right side below the level of the 9th thoracic segment, and the vasoconstrictor responses likewise dropped almost to a zero value. There remained only a few small responses such as are elicited in normal subjects by light contact stimuli. It is evident that the lateral spino-thalamic tract was the afferent pathway for the hyperactive vasoconstriction response as well as for the sensory hyperæsthesia.

Group II.—Cases with a " thalamic syndrome " or with extensive cerebral destruction.

Case 11.—Hyperpathia resulting from a thalamic lesion.

F. G., a male aged 26, was admitted under Dr. Gordon Holmes on October 3, 1935. Following an accident there was a gradual onset of left hemiparesis with left sided sensory impairment and paræsthesia. There was a left hemiplegia with a continuous tremor and cogwheel rigidity. This was associated with diminution in cortical forms of sensation and very gross overaction to pain and thermal stimulation. Sensory examination at the time of the experiment revealed the following changes. Cotton-wool felt " rasping " on the left side. There was diminution to light touch on the left side of the body, measured by von Frey's hairs. Joint sense and two point discrimination were diminished on the left side, but vibration appeared to be normally appreciated. There was marked overaction to cold and pain on the left side of the body. Pin-prick was much more unpleasant, and cold was either " icy " or " scalding " on the left side. The patient winced involuntarily when stimulated on the left, but not on the right. The right side of the body was normal in all respects.

Pin-prick, ice, and pinching stimulation or symmetrical points on the two sides of the body gave equal average vasoconstrictor responses.

Case 12.—Hyperalgesia resulting from thalamic lesion.

G. J., a female aged 36, was admitted under Dr. Gordon Holmes on March 3, 1932. There was a residual hyperalgesia as a result of a vascular lesion in the right thalamus which had occurred seven years previously. When in hospital there was a tremor of the left side of the body, with left-sided paræsthesia. Heat and rough surfaces produced an " uncomfortable feeling " on the left side, that side felt " drawn up " and " tight," and there was a vague constant pain on the left. Pin-pricks and scratching were more unpleasant on the left than on the right, and even moderate heat was painful. Cortical forms of sensation were normal. At the time of the experiment much of this sensory picture had changed, but pin-prick was definitely sharper and more unpleasant above a high threshold on the left, and extremes of heat and cold were more painful on the left side of the body.

The vasoconstrictor response to heat, cold, and moderate pin-prick were equal from both sides of the body, the response to strong pin-prick was over twice as great as on the normal side, but the difference was not statistically reliable.

Case 13.—Hyperpathia, resulting from thalamic lesion.

H. M., a female aged 50, was admitted under Dr. C. P. Symonds, on May 27, 1936. Five years previously she had an embolic accident to the right thalamus, the result of mitral stenosis. She presented the classical picture of the "thalamic syndrome," with spontaneous pain, left hemiplegia, and sensory changes. The spontaneous pain was very severe, but the patient could not describe it accurately. On the left side pin-prick was diminished in acuity, but associated with a radiating and most objectionable pain. There appeared to be a raised threshold to pin-prick. Cold was not felt as cold, but as a scalding burning sensation, with a wide radiation. Pressure was accompanied by an unpleasant sickly aching sensation. Light touch gave a "nasty scraping feeling," described at various times as "tickling which is unpleasant," "scratching" and "pins and needles." Two point discrimination, stereognosis, and joint sensation were much diminished. The right side was normal.

Vasoconstrictor responses to pin-prick and cold on the two sides of the body were identical.

Case 14.—Hypæsthesia due to thrombosis of the middle cerebral artery.

T. S., a male aged 44, was admitted under Dr. E. A. Carmichael on September 9, 1935. There was a flaccid hemiplegia on the right, with "partial wasting," following apoplexy nine months previously. There was diminution in the appreciation of light touch, vibration, two point discrimination, and joint sense on the right. Pain was also impaired on that side, and discrimination of thermal difference was diminished. Pin-prick was not sharp on the right side, and did not evoke as much pain as on the normal side.

The vasoconstrictor responses to pin-prick and to ice on the two sides of the body were equal.

Case 15.—Hypæsthesia due to a parietal glioma.

E. W., a male aged 32, was admitted under Dr. D. Denny-Brown on August 1, 1936. He had a progressive flaccid hemiplegia on the left, with "parietal wasting." There was profound sensory loss to all forms of stimuli on the left side. At operation a large subcortical astrocytomatous cyst was found and aspirated where it was nearest the surface, just posterior to the fissure of Rolando.

Sensation at the time of the experiment was as follows: Light touch, vibration, joint movement and two points were appreciated with difficulty throughout the left side. There was absolute astereognosis on the left. Pin-prick was appreciated as touch only, and there was only a slight element of pain present on repeated stimulation. Moderate cold felt colder on the right, and ice did not feel like ice on the left; it evoked only a mildly cool sensation. Heat was appreciated only as warmth on the left when it was hot on the right. The difference between the feeling of pain and thermal sensations on the two sides was very marked.

The vasoconstrictor responses to mild and severe pin-prick and to ice applied to both sides of the body were identical.

Table IV summarizes the data obtained from the study of vasomotor responses in the second group of patients. The results stand in distinct contrast to those of the first group. Although the degree of sensory change was as great as that in the former group of patients, no significant alteration in the magnitude of the vasoconstriction responses was observed. This equality in the response was particularly dramatic in the three patients with the sensory overaction of the thalamic syndrome. Stimuli on the affected side of the body were reported as extremely painful and only by repeated requests could the patients be persuaded to sit quietly and continue the tests. Yet to these stimuli the vasomotor response was no greater than to the same stimuli applied to the normal side where they were endured with no signs of discomfort.

TABLE IV.

Comparison of the vasoconstrictor responses in the second group of patients to stimuli on the normal and affected regions of the body. The symbols are the same as in Tables I and III.

Case	Level of lesion	Direction of sensory change	Stimulus	Normal region	Affected region	Difference	t	P
11	Thalamus	Hyperæsthesia	Strong PP	10·4	11·9	+ 1·5	0·604	0·5
			Cold	13·4	12·4	− 1·0	0·463	0·6
			Pinch	16·7	16·3	− 0·4	0·171	0·8
12	Thalamus	Hyperæsthesia	Weak PP	2·0	2·8	+ 0·8	0·555	0·6
			Strong PP	3·2	8·7	+ 5·5	1·993	0·06
			Hot	1·9	2·2	+ 0·3	0·220	0·8
			Cold	14·4	13·3	− 1·1	0·294	0·8
13	Thalamus	Hyperæsthesia	Strong PP	4·0	3·7	− 0·3	0·186	0·8
			Cold	5·0	4·9	− 0·1	0·042	0·9
14	Cerebrum	Hypæsthesia	Strong PP	10·7	8·0	− 2·7	0·654	0·5
			Cold	14·6	16·5	+ 1·9	0·463	0·6
15	Cerebrum	Hypæsthesia	Weak PP	1·9	1·3	− 0·6	0·741	0·4
			Strong PP	31·6	34·7	+ 3·1	0·524	0·6
			Cold	2·2	2·4	+ 0·2	0·145	0·8

Cases 14 and 15 are obviously not an adequate sample of cerebral lesions and have been included in this series merely to indicate the possible effects of cerebral destruction upon the vasomotor response. The two cases were selected because of the definite and marked hypalgesia. The results obtained showed no difference between the vasoconstrictor responses to stimuli on the normal and affected side of the body, but this finding must be checked by more extensive observations. The cases are valuable, moreover, in presenting in the hypalgesia the converse of the sensory picture of the thalamic syndrome. From the extent of the lesions and the degree of analgesia, it is probable that this sensory change was due to destruction of a part of the thalamus itself or of afferent fibres in proximity to the thalamus.

Considered as a group, the last five cases demonstrate that lesions in the cerebral hemispheres cause no significant alteration in the vasomotor response corresponding to the sensory changes, while in the first group with lesions below the thalamus the vasomotor response varies in the same direction as the subjective sensory response.

Discussion.

The peripheral efferent pathway of the vasoconstrictor response has been shown by Stürup, Bolton, Williams and Carmichael (1935) to be exclusively dependent upon the sympathetic nerves. The diminution in digital volume following sensory stimulation was abolished by section of the sympathetic innervation of the digit and remained unaffected by destruction of the dorsal and ventral root fibres supplying the digit when the sympathetic nerves were intact, as is the case in a cauda equina lesion. Destruction of peripheral sensory nerves rendered it impossible to elicit vasoconstrictor responses from the anæsthetic area. Doupe, Robertson and Carmichael (1937) showed that destruction of the dorsal root fibres in the cauda equina produced a similar result, thus demonstrating that the sympathetic nervous system in man depends for its afferent pathway on the somatic sensory nerve fibres.

Although the extramedullary pathway of the vasomotor arc has been established, its intramedullary course is not accurately known. Ranson and Billingsley (1916, b) have suggested, on the basis of experimental lesions in cats, that the ascending pressor vasomotor pathway in the spinal cord lies in the tract of Lissauer at the apex of the posterior horn. Evidence from the present study, however, demonstrates that the afferent pathway of the vasoconstrictor response is identical with the sensory pathway. Affections of the peripheral sensory nerves, of the dorsal root ganglia, and of the intraspinal tracts which cause increased or decreased sensitivity to somatic stimuli also cause a corresponding increase or decrease in the resulting vasomotor responses.

In the first group of cases, those with lesions of the sensory pathway below the thalamus, the correlation between the degree of sensory disturbance and the alteration in the vasoconstrictor response was striking in every subject. It is true that lesions of the central nervous system in man, however discrete, cannot have the same localizing significance as experimental lesions in animals. Nevertheless, such a correlation makes it extremely likely that the sensory and vasomotor afferent pathways are identical. Furthermore, in both the normal and abnormal subjects, the vasomotor responses varied with the intensity and the subjective appreciation of the stimulus. Were the intramedullary afferent pathway of vasoconstrictor response different from that for pain, it is extremely unlikely that such a correlation would have been found in all these circumstances. Experimental confirmation of this conclusion is given by Case 2, in which an abnormally great vasoconstrictor response was virtually abolished by section of the spino-thalamic tract.

The lack of correspondence, on the other hand, between subjective sensory intensity and vasomotor response in the second group of subjects—patients with thalamic and cerebral lesions—makes it evident that the two pathways are not identical in the cerebrum. In these five cases there was a very profound alteration, both increase and decrease, in sensations evoked by stimuli which were adequate for the vasoconstrictor response, but there was no comparable change in the vasomotor response. Two reasons are possible for this—a divergence of the afferent sensory and vasomotor pathways, or a termination of the vasomotor afferent fibres below the level of the lesions. It is unlikely that the lesions in these five cases would all have spared the afferent vasomotor fibres, with such definite involvement of the sensory pathways. The more probable explanation is therefore that the central arc of the vasoconstrictor response is complete below the level of the cerebrum. Further evidence that the vasomotor arc does not ascend to the cerebrum has been given by Stürup, Bolton, Williams and Carmichael (1935) who showed that diverse lesions of the cerebral hemispheres resulting in hemiplegia caused no change in the vasoconstrictor responses to sensory stimuli. On the other hand, Schwartz (1937) has reported that the removal of the area frontalis agranularis (Area 6 of Brodmann) of the cat's cortex abolishes the galvanic skin response in the contralateral limbs to sensory stimuli such as noise, pinch and pain. Whether this result, which stands in clear contrast to the absence of effect of cerebral lesions in man, will be found due to a difference in the subjects used, in the response studied, or in the cerebral areas involved, must be determined by further observations.

From the present experimental knowledge of the central control of sympathetic activity and from unpublished observations which are being accumulated on the effect of lesions in man it would appear that the vasomotor arc involves the hypothalamus. Since there was no overaction of the vasomotor response corresponding to the sensory overaction in the patients with the thalamic syndrome, it is plausible to postulate that the hypothalamus receives its sensory input by way of collaterals leaving the ascending sensory tract before it terminates in the thalamus, rather than by collaterals of the thalamo-cortical projection fibres. This view receives support from the experiments of Bard (1929) in which it was found that removal of the cerebral hemispheres and most of the dorsal thalamus in cats did not abolish the sympathetic responses characteristic of "sham rage."

The absence of cerebral influence upon the vasomotor response to somatic stimuli does not necessarily imply the absence of any influence upon other forms of vasomotor or sympathetic activity. It is clear that vasoconstrictor responses can be instituted by word association, mental effort, fear and apprehension, and other processes which undoubtedly depend on cortical functioning. Many experimenters, whose investigations have recently been reviewed by Kennard (1937), have found that stimulation of the pre-Rolandic areas gives rise to vasomotor and other sympathetic changes. Moreover, the extirpation of these cerebral areas in animals, or their involvement in pathological lesions in man, may be followed by vasomotor changes in the contralateral limbs as evidenced by an increased or a decreased skin temperature relative to the normal side. The relation of this form of cerebral influence upon vasomotor activity to the absence of such influence upon vasomotor responses to sensory stimuli awaits further experimental study.

The existence of a vasomotor centre in the medulla has long been recognized. Electrical stimulation of the caudal end of the floor of the 4th ventricle in cats has been shown to cause at one point a rise in blood-pressure, and at another point a fall in blood-pressure (Ranson and Billingsley, 1916, a). That the medullary centre is not adequate for mediation of vasoconstrictor responses to sensory stimuli in man, however, is clearly shown by the results of Cases 8, 9 and 10. Lesions of the sensory pathway above the level of the medullary centre caused marked alteration of the magnitude of the vasoconstrictor response. It is likely that the centre in the medulla is concerned with vasomotor regulation in response to vagus and associated afferent impulses and not to somatic stimulation.

If the vasomotor response to sensory stimulation is not affected by thalamic and cerebral involvement of the sensory pathways, it should follow that hysterical anæsthesia and hypnotically induced anæsthesia should be without effect on such responses. Levine (1930) found no change in the galvanic skin response to stimuli in the anæsthetic region of hysterical and hypnotized individuals, but his data was not complete enough for statistical comparison of the size of the responses. Sears (1932), in a more extensive controlled study, measured certain skeletal and sympathetic responses in individuals rendered anæsthetic in one limb by hypnotic suggestion. Although the flinching response and the change in respiratory movements caused by pain stimuli were eliminated by hypnotic anæsthesia, there was no significant alteration in the size of the galvanic skin response or the sphygmographic record of the pulse. More specific study of vasoconstrictor responses under hypnotic anæsthesia will be published in the near future.

The results of the present study have bearings on the theory of emotion. According to the well known James-Lange conception, the experienced emotion is the perception of the muscular and visceral changes which occur in response to the emotional stimulus. The quality and the intensity of the emotion will vary with the nature and magnitude of the bodily changes. A correlation between the size of the sympathetic response and the reported intensity of pain was found in the normal subjects and in the patients of Group I whose lesions involved the sensory pathway below the level of the thalamus. This correlation does not imply an *essential* relationship, however, for in Cases 11 to 15, the exaggerated or diminished sensory experience was not accompanied by any corresponding alteration in the magnitude of the vasomotor reaction. This result supplements the already large body of experimental data adverse to the James-Lange theory (Cannon, 1927).

Prominent in recent discussions of the neurological mechanism of emotion is the conception that thalamic function determines the nature of emotion and emotional response subject to inhibitory control by the cortex. Two observations provide the foundation of this conception: (1) that decorticate animals respond to painful or emotional stimuli by an exaggerated reaction involving a generalized sympathetic discharge (Bard, 1929); and (2) that in certain patients exhibiting emotional overreaction to painful stimuli (thalamic syndrome), it has been found that the pathological lesion sometimes involves the region of the thalamus, and presumably interrupts a cortico-thalamic inhibitory pathway (Head, 1920). The first fact deals only with observed behaviour response; the second, only with the reported sensory experience. If the two observations refer to the same process, however, it should be possible to demonstrate an increased sympathetic response in patients with the emotional overreaction of the thalamic syndrome. In the three patients of this type studied by us (Cases 11, 12, 13), there was clear evidence to the contrary. No exaggeration of vasomotor reactions to stimuli which evoked intense sensory unpleasantness was observed. It is evident that the exaggerated "emotion" of decorticate animals and of patients with thalamic syndrome is not the same thing. Other evidence of a clinical nature has cast serious doubt on the explanation of the thalamic syndrome as a release from cortical inhibition (Wilson, 1927; Davison and Schick, 1936).

SUMMARY.

The central neural mechanism of the vasoconstrictor response to sensory stimuli has been investigated by plethysmographic recording of vasomotor changes in five normal subjects and fifteen patients with discrete lesions of the nervous system involving the sensory pathway.

It has been found that in normal subjects the vasoconstrictor responses to equal stimuli on symmetrical skin areas are equal, and that they vary directly with the intensity of the stimulus.

In ten subjects with lesions of the sensory pathway below the level of the thalamus the vasomotor response varied directly with the change in the subjective appreciation of the stimuli, while in five subjects with lesions of the sensory tracts in the thalamus or cerebrum, there was no effect on magnitude of the vasoconstrictor response.

The evidence presented suggests that in man the ascending pathway for the vasomotor response to somatic stimulation is the spino-thalamic tract, and that the vasomotor reflex arc is complete in the brain-stem below the level of the sensory thalamus.

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VASOMOTOR CONTROL OF CEREBRAL VESSELS.

BY HENRY S. FORBES AND STANLEY S. COBB.

(Boston).

VASOMOTOR regulation in the brain is different from that in other organs. In the past, investigators have laid great emphasis on the passive behaviour of vessels in the brain. Bayliss (1895) wrote:—

> ". . . . there is no adequate evidence that the cerebral vessels have any vasomotor control ; the importance of the brain is such that its circulation is regulated by the whole of the rest of the body, which is caused to accommodate itself, by constrictor or dilator nerves, to the needs of the brain. (Bayliss, Hill and Gulland, 1895.)

The latter part of this statement, certainly, is confirmed by recent careful observations—those, for example, of Rein (1931) and of Bouckaert and Heymans (1933, 1935) who show in detail how the carotid sinus and other reflexes cause a redistribution of blood in favour of the brain. In man satisfactory proof of the existence of vasomotor control of cerebral vessels is still lacking (Carmichael, Doupe and Williams, 1938).

During the past few years, however, workers in different laboratories, using different experimental methods, have obtained convincing evidence that in animals cerebral vasoconstrictor nerves do exist, but that they exert slight influence on arterial calibre (Forbes and Wolff, 1928 ; Forbes, Finley and Nason, 1933) or on cerebral blood flow (Schmidt, 1934-35, 1935-36 ; Noyons, Westenrijk and Jongbloed, 1936 ; Norcross, in press ; Bouckaert and Jourdan, 1936, a) compared with the effect of constrictor nerves in other organs. Many other workers are in agreement with these findings (Finesigner and Putnam, 1933 ; Franke and Seager, 1932 ; Aske-Upmark, 1935 ; Thomas, 1936 ; Tinel and Ungar, 1936 ; Fog, personal communication). A vasodilator mechanism has also been described (Cobb and Finesinger, 1932 ; Chorobski and Penfield, 1932 ; Forbes, Nason, Cobb and Wortman, 1937). Furthermore, improved histological methods have demonstrated beyond question the presence of nerve fibres—myelinated and non-myelinated—on the cerebral vessels and meninges both in animals and in man (McNaughton, 1938).

To get a clear idea of the part played by the vasomotor apparatus, it may be well to review the many factors which regulate the blood flow through the brain. Within the past three years information has been obtained which for the first time permits a reasonably accurate summary of these factors. They may be divided into two main groups—indirect and direct, or extracerebral and cerebral (Table I).

TABLE I.

FACTORS REGULATING BLOOD FLOW IN BRAIN.

Extracerebral
  Systemic Arterial Pressure
Cerebral
  Active Changes in Arterial Calibre due to:—
    A. Direct trauma.
    B. Chemical changes in arterial blood—CO_2 ; drugs.
    C. Asphyxia of tissues from slow blood flow.
    D. Local neuron activity—local increase in flow.
    E. Vasoconstrictor nerves—sympathetic.
    F. Vasodilator nerves—parasympathetic.
  Passive Changes in Arterial Calibre.

EXTRACEREBRAL FACTORS.

The Systemic Arterial Pressure.

This factor appears to dominate all others. The arterial pressure, in turn, depends on complex reflexes from the cardiovascular centres of the central nervous system, the carotid sinuses and other reflex mechanisms. These reflexes, therefore, play a vital part in controlling the supply of blood to the brain (Bouckaert and Heymans, 1933; Weiss and Baker, 1933). Other factors contribute to this end: the resistance of arterioles throughout the body, the amount of venous blood returned to the heart and the state of the heart itself.

CEREBRAL FACTORS.

Active Changes in Calibre of Cerebral Arteries.[1]

Such changes in calibre, due to changes in tonus of the arterial walls, may overcome moderate or gradual fluctuations in arterial pressure (Fog, 1934: Forbes, Nason and Wortman, 1937; Fog, 1937). Thus, when active changes occur, we usually find arterial constriction following a rise in blood-pressure and dilatation following a fall. An explanation for this inverse relationship between arterial calibre and intravascular pressure is suggested below in paragraph (*c*).

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[1] By the term "active changes in calibre" we mean changes due to alterations in the state of contraction and relaxation of the muscle fibres of the arterial walls (tonus). The fact that the arteries do not behave like inert collapsible tubes (varying in size directly with the internal pressure) indicates that active work is performed by their walls.

Active changes in calibre result from the following conditions:—

(*a*) Direct trauma to vessel walls.

(*b*) Changes in chemical composition of the arterial blood. Variations in tension of arterial CO_2 are of first importance, for CO_2 strongly dilates all cerebral vessels (Wolff and Lennox, 1930). Many drugs (nitrites, alcohol) and inhaled gases (CO, H_2S) act in a similar fashion.

(*c*) Asphyxia of the tissues due to slow blood flow (termed by Van Slyke "stagnant anoxia"). This condition in the brain may result from general or local causes: low blood-pressure, high intracranial pressure or occlusion of vessels supplying the brain. In all of these states we have seen the cerebral arteries dilate (Forbes, Nason and Wortman, 1937). Partial compensation for the slowing of blood flow is thus established. The dilatation is probably due to a chemical (asphyxial) effect on the arterial walls,[1] not to a nerve reflex, for it is unaffected by cocaine or by atropine applied locally to the vessels (Forbes, Nason and Wortman, 1937). When the blood-pressure rises again, the relaxed walls may dilate still further for a few seconds, but then (while the pressure is still rising) constriction steadily takes place as the asphyxial condition is relieved by the more rapid flow.

(*d*) Regional activity of the brain. There is evidence that active areas of grey matter have a local vasodilatation (Cobb and Talbott, 1937; Feitelberg and Lampl, 1934-35; Gerard and Serota, 1936). This may be due to a local increase in CO_2 or other products of active cellular metabolism.

(*e*) Activity of cerebral vasoconstrictor nerves (sympathetic).

(*f*) Activity of cerebral vasodilator nerves (parasympathetic).

These last two conditions have less effect on cerebral blood flow than the chemical conditions mentioned under (*b*), (*c*) and (*d*).

Passive Changes in Calibre of Cerebral Arteries.[2]

Distension or slight narrowing may occur during abrupt fluctuations of blood-pressure. Such changes in calibre are obviously due to mechanical causes. These passive changes in calibre are transient, however, and slight in extent, unless the vessel walls are in a relaxed state. In that case, a rise in intravascular pressure may cause extreme dilatation.

---

[1] A possible explanation for this effect may be the following: the muscle fibres within the arterial walls produce CO_2 as a result of their own metabolism. The CO_2 diffuses into the lumen and is carried off by the blood. When the rate of blood flow is diminished the tension of CO_2 increases in the muscular coats, owing to delayed elimination through the lumen. The increased tension of the gas relaxes the muscle fibres and allows the intravascular pressure to dilate the artery.

[2] These changes, although ocurring within the brain, are really of extracranial origin, for they depend on changes in arterial pressure.

The main object of this paper is to discuss the neural vasomotor mechanism of the brain and to present in some detail the results of recent experimental work. Various methods have been used, both indirect and direct. Each method has its advantages and its drawbacks. These have been reviewed critically by Bouckaert and Jourdan (1936, a). The recent indirect evidence will be given first.

Vasoconstriction.

Schmidt (1934-35, 1935-36) and Schmidt and Pierson (1934), using a thermo-electric method, obtained evidence of retarded flow on stimulation of the cervical sympathetic nerve. This effect was noticeable chiefly in the parietal cortex, less in the hypothalamus and still less (or doubtful) in the medulla. The change in flow appeared to be independent of changes in blood-pressure, but the extracranial circulation was not excluded in these experiments.

Noyons, Westenrijk and Jongbloed measured changes in blood flow with a Gibbs' thermo-electric recorder imbedded in the cortex of dogs, cats and rabbits (the latter non-anæsthetized). The results confirm those of Schmidt: stimulation of the cervical sympathetic trunk caused a slight retardation of the cerebral blood flow coincident with a strong constriction of the arteries of the ear and a small rise in blood-pressure.

Still more recently Norcross has also completed a careful investigation using similar methods. His results confirm those of Noyons and of Schmidt.

Bouckaert and Jourdan (1936, a), using three different methods, eliminated completely the extracranial circulation by a radical operation, and perfused the isolated head. On stimulation of the cervical sympathetic nerve they obtained evidence of vascular constriction and a reduced flow through the brain. Many investigators using perfusion experiments have obtained similar but less convincing evidence. Their work is summarized by Bouckaert and Jourdan.

In our own laboratory, by the use of a cranial window and microscope, we have observed and recorded the changing diameters of vessels in the pia-arachnoid over the parietal cortex. For this work we have used mostly cats, a few dogs and several monkeys. Our findings, some of them not yet published, may be summarized as follows:—

In a large series of experiments, on more than 300 animals, stimulation of the cervical sympathetic nerve has resulted consistently in constriction of arteries in the pia. We have found that the sympathetic fibres responsible for the reaction pass through the middle ear in close association with the caroticotympanic nerves. The latter serve as pathways for the sympathetic fibres which dilate the pupils (Kuntz, 1934). Sympathetic nerve fibres via the stellate ganglion and vertebral nerves exercise no influence, so far as we could determine, on pial arteries of the parietal region. The time relations and magnitude of the response can be seen in the graphic records.

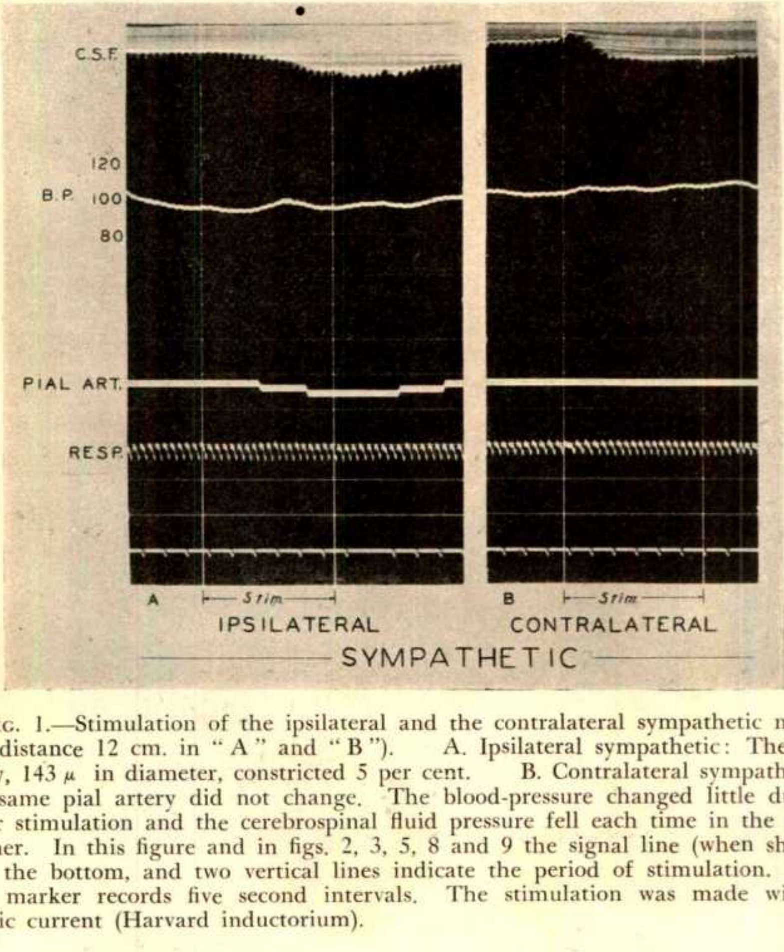


FIG. 1.—Stimulation of the ipsilateral and the contralateral sympathetic nerves (coil distance 12 cm. in "A" and "B"). A. Ipsilateral sympathetic: The pial artery, 143 μ in diameter, constricted 5 per cent. B. Contralateral sympathetic: The same pial artery did not change. The blood-pressure changed little during either stimulation and the cerebrospinal fluid pressure fell each time in the same manner. In this figure and in figs. 2, 3, 5, 8 and 9 the signal line (when shown) is at the bottom, and two vertical lines indicate the period of stimulation. The time marker records five second intervals. The stimulation was made with a faradic current (Harvard inductorium).

The chief characteristics of this arterial constriction are as follows:—

(1) It is strictly ipsilateral, that is, the vasoconstriction occurs only on the same side of the head as the nerve stimulated. No exceptions to this rule have been observed (fig. 1).

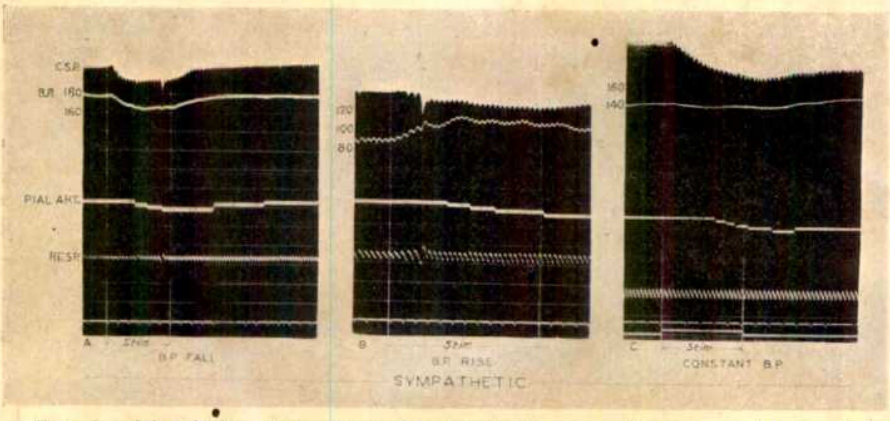


FIG. 2.—Stimulation of the cervical sympathetic nerve, showing a falling, a rising and a constant blood-pressure during the stimulation (coil distance 13 cm. in "A" and 12 cm. in "B" and "C"). A. The blood-pressure (178 mm. Hg.) fell 14 mm.; and the pial artery, 169 μ in diameter, constricted 8 per cent. B. The blood-pressure (88 mm. Hg.) rose 28 mm.; and the pial artery, 117 μ in diameter, constricted 11 per cent. C. The blood-pressure remained constant (at 140 mm.) throughout the stimulation; and the pial artery, 114 μ in diameter, constricted 14 per cent. The cerebrospinal fluid pressure fell with each stimulation.

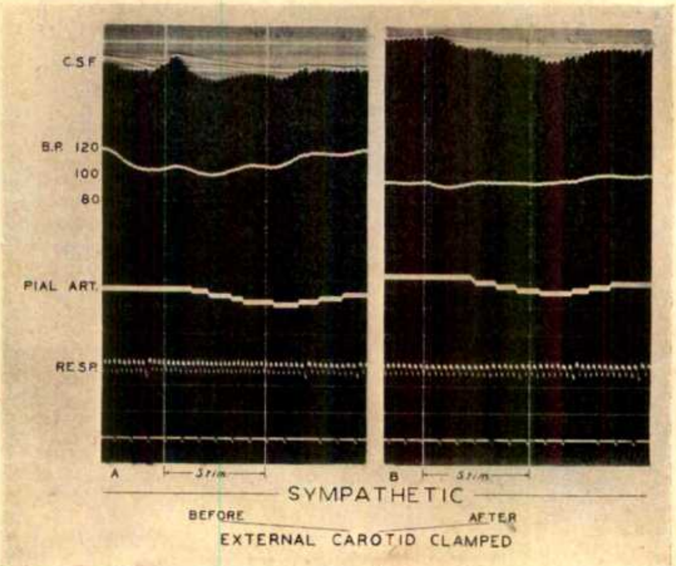
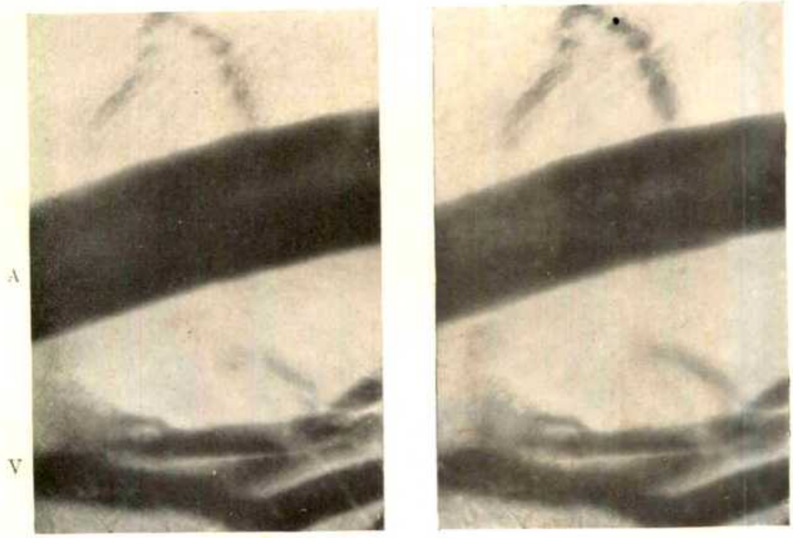


FIG. 3.—Stimulation of the cervical sympathetic nerve before and after the ipsilateral external carotid artery was clamped (coil distance 13 cm. and angle 15° in both "A" and "B"). A. The pial artery, 169 μ in diameter, constricted 10 per cent. B. The pial artery, 186 μ in diameter, constricted 7 per cent. The cerebrospinal fluid pressure fell with each stimulation, and the blood-pressure changed little during either stimulation.

PLATE IX.

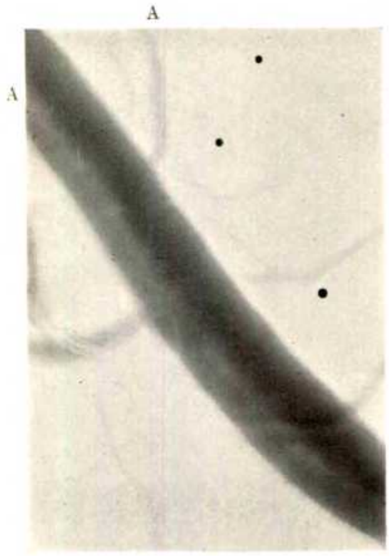


(a) (b)

FIG. 4.

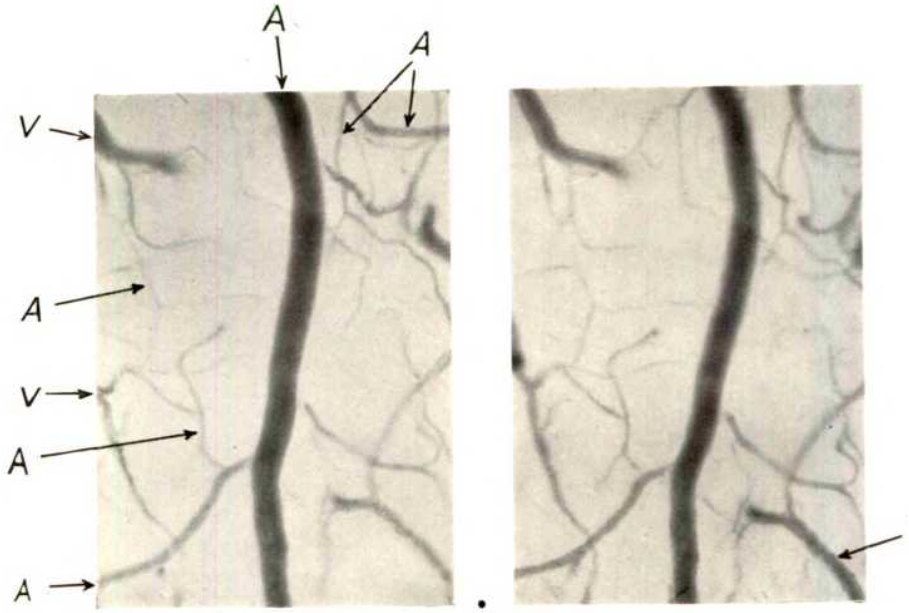
To illustrate article by Henry S. Forbes and Stanley S. Cobb.

PLATE X.



(a) (b)

FIG. 6, a.

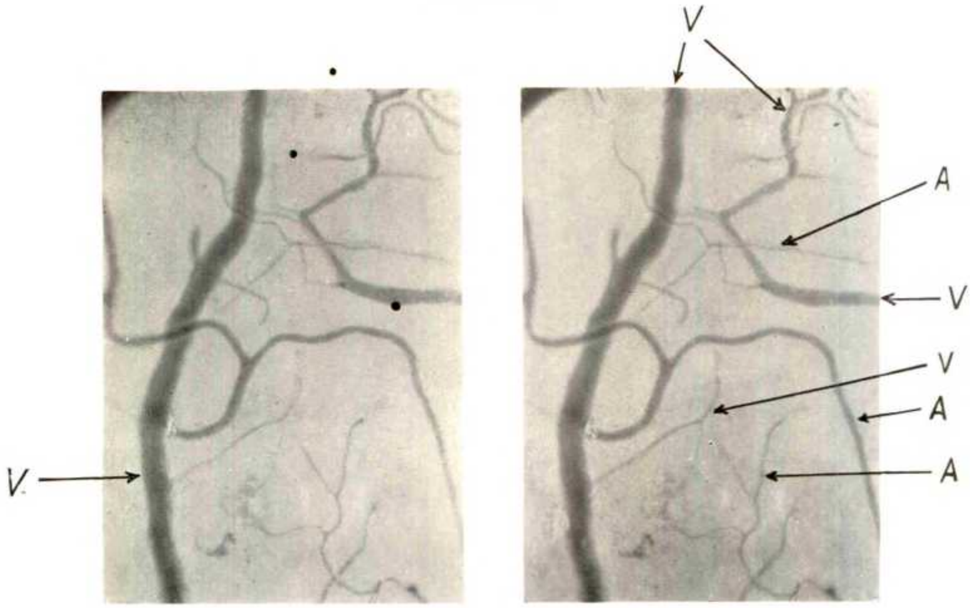


(a) (b)

FIG. 6, b.

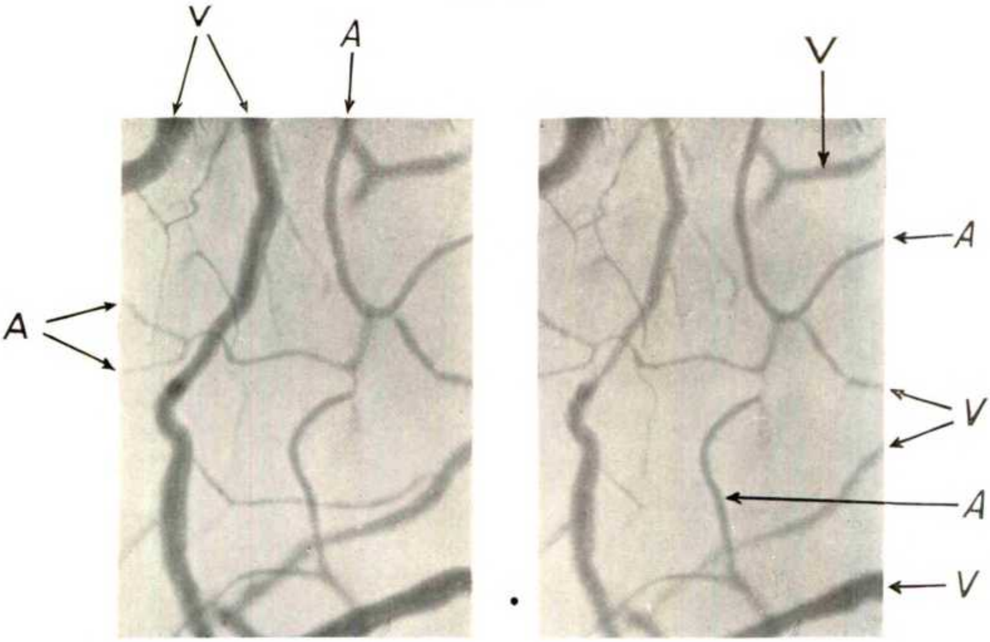
To illustrate article by Henry S. Forbes and Stanley S. Cobb.

PLATE XI.



(a) (b)

FIG. 6, c.



(a) (b)

FIG. 6, d.

To illustrate article by Henry S. Forbes and Stanley S. Cobb.

(2) It appears to be independent of changes in systemic arterial pressure, since it takes place when the latter is rising, is falling, or is constant (fig. 2).

(3) It occurs even when the greater part of the extracranial circulation is eliminated by clamping one or both external carotid arteries (fig. 3).

(4) It occurs in the completely isolated head, perfused through the carotid arteries of another animal. This fact as well as its unilateral character show definitely that humoral substances are not responsible for the reaction (Pool, Forbes and Nason, 1934, a) (fig. 4).

(5) It is abolished by the previous application of cocaine, novocain, or ergotamine locally to the pial arteries under observation (fig. 5). Such procedures would be expected to inactivate nerve elements in the walls of these vessels. The action of ergotamine confirms the fact that the nerves involved are of sympathetic origin.

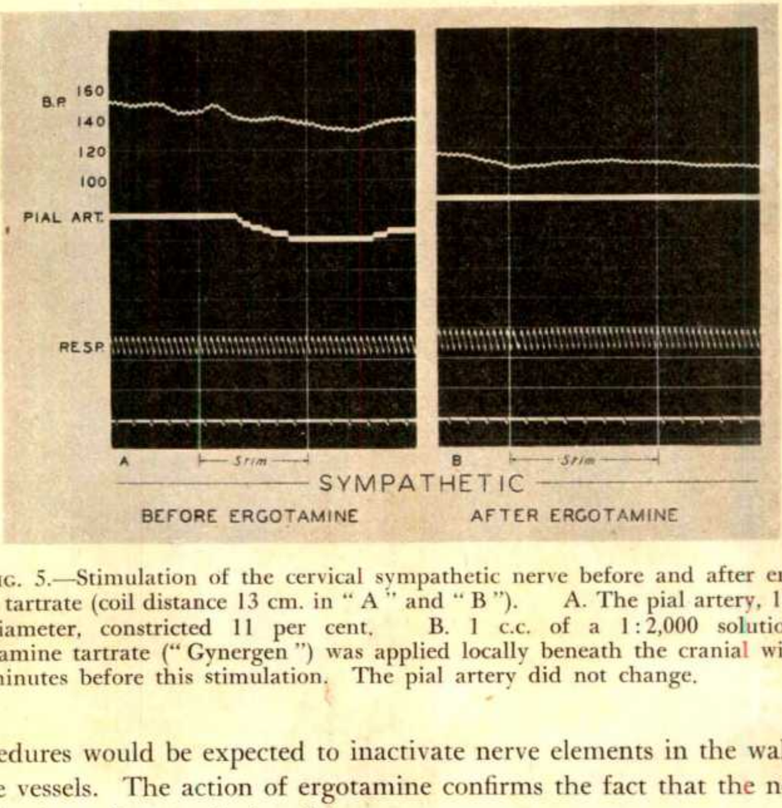


FIG. 5.—Stimulation of the cervical sympathetic nerve before and after ergotamine tartrate (coil distance 13 cm. in "A" and "B"). A. The pial artery, 182 μ in diameter, constricted 11 per cent. B. 1 c.c. of a 1:2,000 solution of ergotamine tartrate ("Gynergen") was applied locally beneath the cranial window six minutes before this stimulation. The pial artery did not change.

(6) It has been observed consistently only with arteries larger than 50 μ in diameter (fig. 6). With the smaller arterioles and capillaries no consistent change in calibre has been seen. It is interesting that Penfield (personal communication) found histological evidence of nerve fibres only on arteries above this size.

(7) The amount of constriction is small—an average narrowing of only 8 per cent. has been observed.

(8) Compared with the vasoconstriction observed in other organs, that in the brain is slight. When the cervical sympathetic nerve is stimulated, arteries in the skin constrict ten times as much as those in the pia (fig. 7) and in the dura the arteries constrict almost eight times as much (Pool, Forbes and Nason, 1934, b).

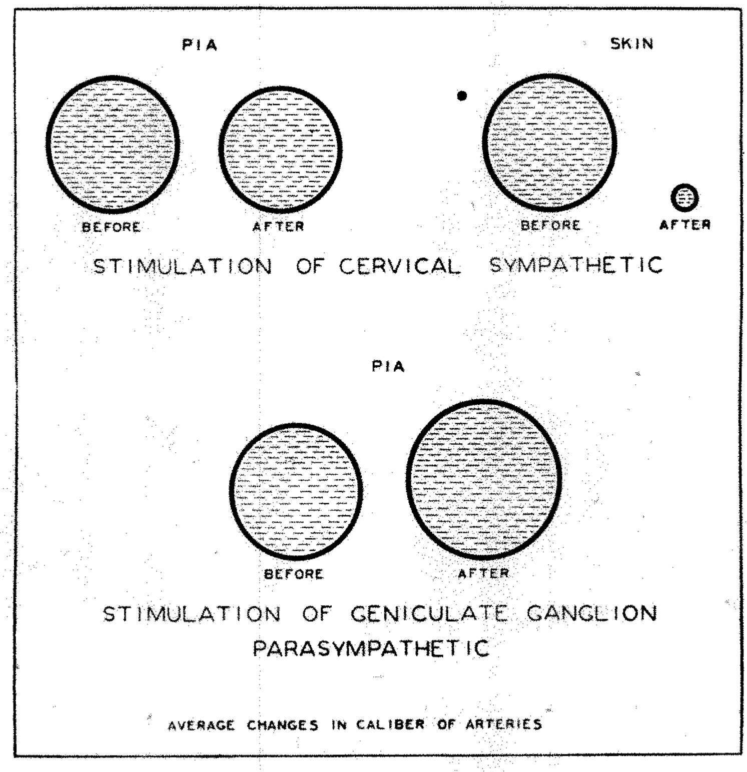

PIA
SKIN
BEFORE
AFTER
BEFORE
AFTER
STIMULATION OF CERVICAL SYMPATHETIC
PIA
BEFORE
AFTER
STIMULATION OF GENICULATE GANGLION
PARASYMPATHETIC
AVERAGE CHANGES IN CALIBER OF ARTERIES

FIG. 7.—The circles are drawn to show the average changes in the cross-sectional area of arteries after stimulation of the cervical sympathetic nerve and after stimulation of the geniculate ganglion. The averages were obtained as follows: Stimulation of cervical sympathetic — *Arteries of pia*: 100 stimulations (30 cats and 1 monkey). Average diameter before stimulation was 169 μ Average constriction was 8 per cent. *Arteries of skin*: 10 stimulations (2 cats and 1 monkey). Average diameter before stimulation was 182 μ. Average constriction was 80 per cent. Stimulation of geniculate ganglion (parasympathetic)—*Arteries of pia*: 115 stimulations (20 cats). Average diameter before stimulation was 195 μ Average dilatation was 16 per cent.

This accumulated evidence seems fairly complete. Some of our observations, however, are at variance with the usual picture of vasomotor innervation, and no satisfactory explanation has yet been found for these atypical reactions.[1]

When the cervical sympathetic trunk is cut, and the superior cervical ganglion removed, we have seen no subsequent dilatation of the pial arteries that we were watching under the window.

When cocaine is injected intravenously there is no evidence of increased sensitivity of the sympathetic vasoconstrictor reaction in the pia, such as Rosenblueth and Cannon have found elsewhere.

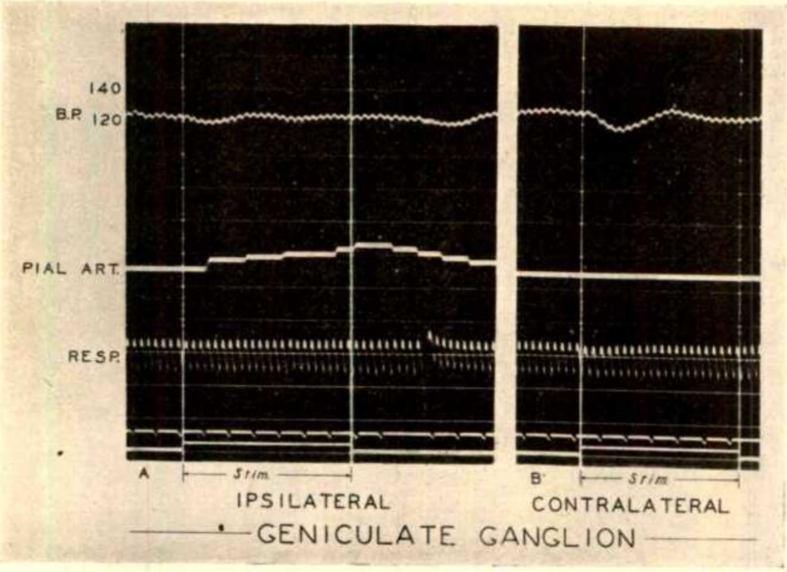


FIG. 8.—Stimulation of the ipsilateral and the contralateral geniculate ganglia (coil distance 13 cm. in "A" and "B"). A. Ipsilateral geniculate ganglion. The pial artery, 162 μ in diameter, dilated 12 per cent. The blood-pressure (124 mm. Hg.) remained nearly constant throughout the stimulation. B. Contralateral geniculate ganglion. The pial artery, 159 μ in diameter, did not change in calibre. The blood-pressure (128 mm. Hg.) fell 12 mm.

No increased sensitivity of the arteries follows denervation. When the superior cervical and stellate ganglia are removed and suitable time is allowed for degeneration of the nerve endings, adrenalin applied locally to the pial arteries causes no greater constriction than it does in the normal animal (White and Forbes, unpublished).

The venules in the pia constrict as much as, or more than, the small arteries when adrenalin is applied locally. Also, the venules sometimes constrict in response to stimulation of the cervical sympathetic nerve (fig. 6, d).

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[1] In recent experiments we have found that atropine solution (1 or 0·5 per cent.) applied locally to the vessels abolished the constriction due to sympathetic nerve stimulation.

Vasodilatation.

Evidence of a vasodilator innervation was first obtained in a joint experiment with Penfield conducted in our laboratory (Cobb and Finesinger, 1932; Chorobski and Penfield, 1932). On a sympathectomized monkey it was shown that stimulation of the facial nerve near the medulla oblongata caused dilatation of pial arteries in the parietal cortex. This reaction occurred only on the same side of the head as the nerve stimulated.

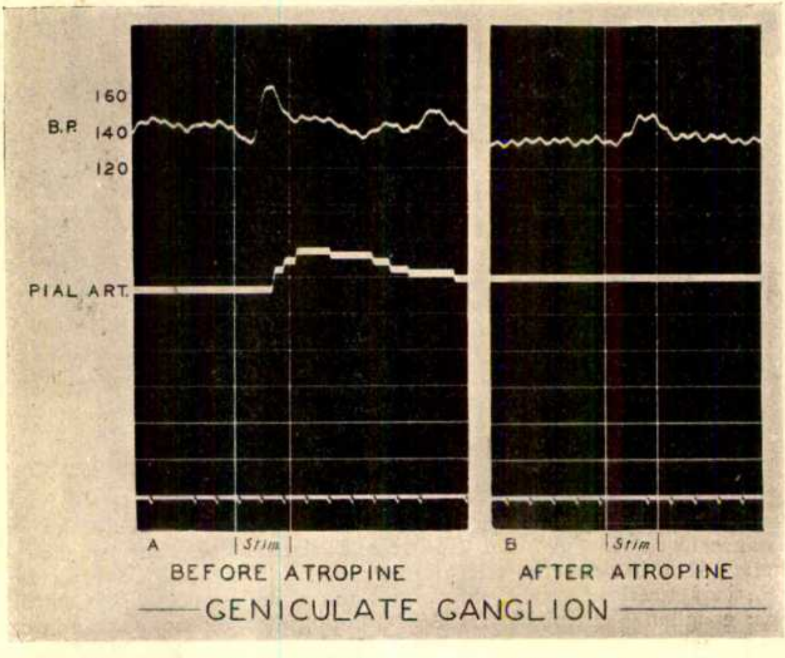

FIG. 9.—Stimulation of the geniculate ganglion before and after local atropine (coil distance 13 cm. and angle 20° in "A" and "B"). A. The pial artery, 182 μ in diameter, dilated 14 per cent. B. 1 c.c. of a 0·5 per cent. solution of atropine sulphate was applied locally beneath the cranial window eighteen minutes before this stimulation. The pial artery, 188 μ in diameter, did not change. The blood-pressure rose promptly during each stimulation.

The further evidence may be summarized as follows:—

Anatomical and histological work by Chorobski and Penfield shows that nerve fibres pass from the facial nerve through the geniculate ganglion and the great superficial petrosal nerve to the carotid nerve ascending the internal carotid artery.

Physiological experiment shows that:—

(1) Stimulation of the facial nerve at the geniculate ganglion causes prompt dilatation of arteries in the pia-mater of the parietal region (Forbes, Nason, Cobb and Wortman, 1937) (fig. 7). In these experiments the facial nerve was cut between the point of stimulation and the medulla.

(2) This reaction is always ipsilateral in character[1] (fig. 8).

(3) Vasodilatation occurs when the blood-pressure is normal at the beginning and remains nearly constant throughout the period of stimulation. This is important, because it has been found that if the systemic arterial pressure falls below a certain critical level the pial arteries always dilate as a consequence of the retarded blood flow.

(4) Local applications of cocaine and of atropine abolish this reaction, though they have no effect on the dilatation due to low blood-pressure. This action of atropine is especially significant since it indicates that parasympathetic nerve elements are involved (fig. 9). Ergotamine (locally) does not affect the reaction.

These observations have yet to be confirmed by other workers using different experimental methods.

COMMENT.

In regard to the functional importance of the cerebral vasomotor mechanism the evidence at hand warrants only a few suggestions. Since it is more effective in some parts of the brain than in others it may aid in diverting the blood from one region to another; it may help arteries to regain their normal calibre, as after extreme dilatation, and it may limit undesirable fluctuations and thus aid in maintaining a steady rate of flow through the brain. But there is no evidence from experimental work to show that it can cause the arteries to shut down sufficiently to bring about ischæmia.

SUMMARY.

The former confusion regarding regulation of blood flow within the brain and its meninges has been clarified by recent experiments carried on independently in different laboratories. To-day there seems to be substantial agreement on several points; that an intracerebral regulation does exist; that in this regulation chemical agents (especially CO_2) play a major part; that cerebral vasoconstrictor nerves are present but that they are only about one-tenth as effective in the pia as the vasoconstrictor nerves are in the skin; that vasoconstrictor nerves are distributed unequally to different parts of the brain. Evidence has been obtained also for the existence of cerebral vasodilator nerves.

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[1] It was thought at first that the vagal centre in the medulla was somehow connected with the facial nerve pathway for dilator impulses to the pial arteries. Later it was found that the bilateral dilatation of these vessels, which follows vagus stimulation, was caused by the fall in blood-pressure, and was distinct from the reaction caused by stimulation of the facial nerve.

With so many regulatory mechanisms one might expect frequent changes in vessel calibre and in blood-flow, even under resting conditions. Such changes do not occur normally. The capillaries, at least in the pia, appear to be always open, the arterioles do not change in size appreciably and the flow is remarkable for its steadiness.

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LEGENDS FOR PLATES IX, X, XI.

FIG. 4.—Photomicrographs of pial vessels in the isolated head taken before and after stimulation of the ipsilateral sympathetic nerve in the isolated head (coil distance 12 cm.). The pial artery, 322 μ in diameter, constricted 12 per cent. In this figure and in fig. 6 the photomicrographs were taken with a Leica camera; Persenso film, objective × 10, ocular × 10. "A" indicates arteries or arterioles, and "V" indicates veins or venules. (*a*) Before stimulation. (*b*) After stimulation.

FIG. 6.—Photomicrographs of pial vessels taken before and after stimulation of the ipsilateral sympathetic nerve in four different experiments (coil distance 13 cm. in "A," 11 cm. in "B," 12 cm. in "C" and "D"). A. The artery, 188 μ in diameter, shows definite constriction. (*a*) Before, and (*b*) after stimulation. B. The largest artery in the field, 62 μ in diameter, shows a definite constriction. Some of the veins and small arterioles constricted slightly, others appear to be larger. The photomicrograph taken after the stimulation was not properly focused and the photographic field was shifted slightly. Therefore, it is difficult to be sure about the smallest vessels. (*a*) Before, and (*b*) after stimulation. C. The venules and arterioles changed little, if at all, in this experiment. However, in the same experiment, larger arteries constricted in the characteristic manner after stimulation of the sympathetic nerve. (*a*) Before, and (*b*) after stimulation. D. The veins and venules show a marked constriction. The small arterioles also constricted in this experiment. (*a*) Before, and (*b*) after stimulation.

NOTICES OF RECENT PUBLICATIONS.

Ueber die Untersuchung der musikalischen Funktionen bei Patienten mit Gehirnleiden, besonders bei Patienten mit Aphasie. By H. J. USTVEDT. Helsingfors. 1937. *Act. Med. Scand. Supplement,* 86. Mercators Tryckeri. Pp. 737. (With French and English summaries.)

The function of language occupies a special rank of obscurity in the provinces of both normal and morbid physiology. Light shed from any angle, however oblique, is especially welcome if it can in any way illumine certain aspects of aphasia. The role of the musical faculty in speech disorders, though hitherto somewhat neglected, possibly for reasons of technical difficulty, suggests a possible line of assault upon the major problem. This present monograph of Ustvedt's is therefore twice welcome: first because it attacks an obscure but potentially important subject and secondly because it successfully emerges as a detailed yet shrewdly reasoned treatise. Previous contributions are singularly speculative and unhelpful, being largely concerned with isolated cases, inadequately studied—especially with regard to the general psychological state. (Exceptions must be made in the case of Henschen and Feuchtwanger.) It is interesting to find that impaired musical function seems almost always to be associated with other psycho-somatic disorders—especially of speech ; pure musical defects do not appear to have been recorded as isolated phenomena. The author offers a number of suggestions for future research and demands a more systematic routine examination of musical function in normal as well as aphasic subjects. He points out that music must not be regarded as a mere appenage of speech, but rather as a totally distinct faculty which, though perhaps possessing a common origin, has early parted ways, losing almost all traces of symbolic purpose. A close and interesting discussion of the psychological nature of musicality is followed by a clinical section. The author's material comprises nineteen cases, mainly of left-sided cerebral lesions. The case-records are very carefully analysed with sympathetic yet critical reference to the modern conceptions of aphasia due to van Woerkom, Goldstein, and others. A lowering of the general emotional level was demonstrable in the musical faculty also. Musical defects do not necessarily accompany an abasement of the general intellectual capacity, and severe aphasia may occur with a relatively unimpaired musical function. From his close scrutiny of the data, Ustvedt has to conclude that our knowledge is still far too superficial to permit any generalizations as to the pathology of musical function. Questions of localization must also remain in the air, although it is interesting to note that in every patient with symptomatic defects of musical function there has been a lesion in the left hemisphere. One must bear in mind, however, that such material is of a selected character.

Ustvedt's monograph is undoubtedly the most important contribution to this aspect of the problem of aphasia.

Chemistry of the Brain. By Irvine H. Page. London: Ballière, Tindall and Cox. Pp. 444. Price 34s.

The chemical changes occurring in the brain in disease offers a new field of research which has but recently received any serious consideration. The author in this extremely well-written and fully documented book has attempted to collect all the recent work on this subject, together with a detailed account of the chemistry of those substances that occur normally in the brain.

These various chemical substances have been discussed in a series of chapters, the latter part of each chapter containing the work that has been undertaken in various diseases in relation to such substances.

Physical chemistry and oxidation processes have been treated in a similar manner. One rather noticeable feature is the relative absence of discussion on changes found in organic nervous disease, but this is explained by the surprising lack of reliable original work.

A large number of observations have been made in mental disorders and these are critically reviewed by the author. For the most part he has very ably discussed all the material at his disposal.

One short chapter on the Brain and Thought, however, is hardly related to brain chemistry.

This work is a comprehensive survey and will be of great value to those who are interested in this subject.

Occupational Treatment of Mental Illness. By J. Ivison Russell. London: Ballière, Tindall and Cox. 1938. Pp. 231. Price 6s.

This eminently practical handbook will be welcomed by all those who may be responsible for the care in institutions of patients suffering from neurosis or psychosis. It deals with the general principles which underlie occupational therapy, the adaptation of this therapy to particular situations and full practical details as to its organization and carrying out.

La Méthode Psychanalytique et la Doctrine Freudienne. Par Roland Dalbiez. Bibliothèque de Philosophie Médicale. Tome I, Exposé, pp. 656. Tome II, Discussion, pp. 528. Paris: Desclée de Brouwer. 1936. 50 Fr. each vol.

The author, who brought to the examination of psycho-analysis a philosophical training and outlook, offers here something more original and useful than the customary arguments or descriptions, wearisome in their sameness. His experience of the subject was gained in the clinic of Professor Claude, who contributes a preface. The volumes are of unequal merit. The first and less satisfying one, which the author prefers to call a *mise-en-valeur* of psycho-analysis, does not take account of modern developments of the subject, which, at any rate for English workers, are implicit in their method ; introjection, for example, is barely mentioned, if at all. The exegetical second volume, therefore, in spite of its admirable and temperate review of the fundamental issues, especially those of a metaphysical nature, neglects the difficulties which the neo-Freudians know only too well: the divergencies of therapeutic method, interpretation and general doctrine which now make libidinal development, the psycho-analysis of children, and female sexuality such controversial issues. Doctrine is less separable from method and more important than Dr. Dalbiez believes ; this distinction, on which he insists, is scarcely tenable unless the treatment of neurosis in adults is the only end in view. His apologia could not be as persuasive as it is, if the doctrinal aspect and the more recent modifications and expansions of psycho-analysis had been fully handled.

Le Systeme Nerveux Vegetatif. Par J. Tinel. Paris: Masson et Cie. 1937. Pp. 847. Price 160 Fr.

This exhaustive monograph from the authoritative pen of Professor Tinel deals in detail with the anatomy and physiology of the vegetative nervous system in the light of the most recent knowledge. The pharmaco-dynamic relations of the system to the ductless glands are fully described, and the formerly debated role of the system to muscle tonus is discussed.

Further chapters deal with the chief syndromes of the system, and their treatment.

The monograph forms a valuable work of reference on its subject. It is admirably illustrated with anatomical diagrams and clinical photographs.

Psychological Studies of Human Variability. Edited by Walter R. Miles. Psychological Monographs: Dodge Commemorative Number. Princeton: Psychological Review Co. 1937. Pp. 415. Price $4·50.

This volume of original papers is intended to commemorate the forty years of work in psychology by Professor Raymond Dodge. His earlier research into eye-movements and his lifelong concern with this subject are reflected in a number of detailed studies on visual function covering such topics as the effect of drugs on optic nystagmus, conditioned eyelid responses, the form of the vestibular eye-movement response in man, and the functional basis of spontaneous nystagmus. There are also many experimental studies dealing with the relation of muscle tone to vibratory sensibility, the adaptation times of the special senses, inhibition, and individual variations in memory and in sensitivity to vertical motion of the body. Professor Dodge's influence and activities at the Yale Institute of Human Relations may be traced in the investigations of children, coming partly from Professor Arnold Gesell and his associates, and in the more theoretical papers by Professor Kahn and others interested in medical, social or educational psychology.

SEPTEMBER, 1938

BRAIN.

PART 3, VOL. 61.

PICK'S DISEASE—A SPECIFIC TYPE OF DEMENTIA.

BY IRA C. NICHOLS AND WALTER C. WEIGNER.

(*Butler Hospital, Providence, R.I.*).

PICK (1892) first described certain progressive dementias showing lack of initiative, aphasias, and finally a vegetative existence terminating in a relatively early death from intercurrent infection. At first he thought of these cases as simple senile dementias, but subsequent observers, after careful histological examinations of autopsy specimens, concluded that the condition required a separate classification, and to it they gave the name " Pick's disease."

Although the subject has obtained considerable Continental attention, there has been a relative scarcity of reported cases in the English and American literature. The present writers believe that the disease is probably much more common than the paucity of reported cases seems to indicate, and hope that the résumé of the condition and the case to be reported herewith will serve to further emphasize this condition as a specific type of brain degeneration with symptoms which differentiate it from other types of dementia. No definite ætiology has been established for this condition. It is perhaps an heredo-degenerative disease. This view is considered the most probable by Grünthal (1930). He notes that the disease has previously been reported as occurring in sisters, and adds two cases of his own in brothers. Thorpe (1932) describes a case in a woman whose father's brain, at autopsy, had shown an unusual degree of atrophy, and considers that he might well have had Pick's disease, although the diagnosis of senile dementia had been made at the time of his death. Familial mental disease is frequently noted in the case reports. Horn and Stengel (1930), as well as Merritt and Springlova (1932), remark upon many similarities in the pathology of this disease to the changes seen in amaurotic family idiocy. Onari and Spatz (1926) call attention to the fact that there are certain clinical and pathological features that link this condition to Huntington's chorea. Since these last two diseases are definitely known to be hereditary, these similarities suggest an heredo-degenerative ætiology for Pick's disease. Ferraro and Jervis (1936) have more recently made a special study of pathogenesis and decided that heredity could not be implicated. They consider that angiospasm plays an important though not exclusive role.

As to the age of onset, the reported cases have shown their initial symptoms between the extremes of 42 and 72 years, with the sixth decade containing the greater proportion. From the published material to date, it seems that the disease attacks females much more frequently than males, the ratio being approximately two to one. So far as can be determined from the available data, there is no special racial incidence.

Schneider (1929) has arbitrarily divided the clinical course into three stages, which are roughly of equal length. This is perhaps convenient, but we must keep in mind that the disease itself is an uninterrupted process. The onset is usually insidious, often being initiated by slight personality changes that are only appreciated in retrospect. Some of the symptoms of the early mental changes follow: indifference in performance of duties, carelessness in dress, disregard for the usual proprieties, nomadism, petty crime, apathy, failing memory, emotional lability, and motor unrest.

As the disease progresses we see in typical cases the development of characteristic symptoms. These are of the type which we associate with frontal lobe disease. The general character of these symptoms has been well described by Goldstein and Katz (1937). A. Stief (1930) noted a form of response suggesting echolalia, in which a prominent feature was minimum expenditure of ideational effort. In the case to be reported, this was a striking feature also. These individuals in replying to questions simply take the interrogative sentence as given to them, make minimal changes in word order and person, and answer the question in the examiner's own words. It is readily seen that this form of response is the most economical of thought. While well-accustomed acts may be long retained, all desire to vary behaviour spontaneously is lost. Thus as the disease progresses we find that the daily programme becomes stereotyped.

The subject of memory in these cases deserves special consideration. While, in the more familiar dementias, a failure of memory is usually an early prominent symptom, in a typical case of Pick's disease memory may be surprisingly intact in the early stages. While early observers reported a failing memory as an early symptom, subsequent studies revealed that it is not so much memory, itself, that is lost, but rather the use of it in the formation of new ideational material. This has been aptly described by

Kahn and Thompson (1934) as " the loss of memory as a tool." In our case, for example, while the patient superficially gave the appearance of deterioration, she was able to recall events with surprising accuracy when pressed for specific facts. Gordon (1935) brings out this point when, in describing his case, he states, " What is particularly striking is that in the midst of progressing dementia, his memory is to a very great extent preserved." The fact that memory is often long retained in this manner is perhaps one of the chief features which distinguishes Pick's disease from the other dementias.

When the second stage becomes more firmly established, hyperkinesias constitute a prominent symptom. This motor unrest is characterized by purposeless behaviour, such as slapping the thighs, tapping the floor, rocking back and forth, making clucking noises, and many other forms of diffuse stereotyped activity.

Another feature which may appear at this point is the occurrence of forms of aphasia. These may be of any type or combination of types, depending upon the associative area or areas involved. While every form has been reported, loss of speech is probably the most frequent. Horn and Stengel collected a group of cases in which apperceptive blindness was a prominent symptom. As the disease progresses, dementia becomes evident, but psychotic symptoms, such as hallucinations, delusions, confabulation and illusions, are rare.

In the third stage, cortical function is so diminished that the patient gradually sinks into a state of extreme hebetude, from which, finally, there is release by death from some intercurrent disease. While epileptiform seizures may occur late in the disease, they are rare. If they occur early, they speak against a diagnosis of Pick's disease. Throughout, physical signs are notably absent, although extra-pyramidal forms of rigidity may occur near the end. The total duration from the first symptom to the inevitable fatal outcome is generally between three and five years, with the reported extremes of two and twelve years. The case to be reported died nine years after the development of symptoms, which date of onset was well established by careful investigation.

In Pick's disease, laboratory examination of all the body fluids, including the spinal fluid, is negative.

X-ray examination of the skull, itself, may reveal thickening of the vault and that type of hyperostosis which sometimes follows atrophy of the underlying cerebrum. Upon encephalographic examination, the importance of which is stressed by Bumke (1929), we find generally enlarged ventricles, which may show dilatations corresponding to the atrophied portions of the brain. The subarachnoid air is seen lying in irregular masses over the cortex, especially in the frontal regions, and filling the dilated insulæ and the cisterna chiasmatica.

There have been several reviews of the pathology of this condition during the past few years, the most complete being those of Onari and Spatz, of Horn and Stengel, and of Ferraro and Jervis. The findings revealed by necropsy may be outlined as follows: The skull is thick and may show hyperostosis. Plaques of leptomeningitis are frequently seen. The brain itself shows evidence of a more or less diffuse atrophy, with localized, roughly symmetrical areas of marked shrinking. Most typically, this process involves the frontal lobes, the first and second temporal convolutions, the insulæ, and the supra-marginal and angular gyri. The occipital and parietal lobes are occasionally involved. The pre- and post-central areas are usually strikingly spared. The brains frequently weigh much less than 1,000 grms. In Thorpe's case, for instance, the weight was 770 grms. In the reported cases, the left hemisphere has usually weighed less than the right.

Microscopic examination of the affected cortical areas reveals an intense loss of nerve cell elements, which reaches its highest degree in the three upper layers of the cortex. The cells are in part replaced by a strong glial reaction. Those which remain are either shrunken or present a bloated appearance. Although Alzheimer's argentophile inclusion bodies are numerous in Pick's disease, and although their presence in such numbers is one of the criteria upon which the pathological diagnosis is made, their real significance is still a subject of controversy. Williams (1935), for example, maintains that Pick's cells are not dependent on the senium or on specific ætiological agents for their development. von Braunmühl (1930), and Merritt and Springlova have described Pick's cells in cases of Lissauer's dementia paralytica. From these investigations it would appear that Pick's cells can and do occur apart from the entity called Pick's disease. Senile plaques and Alzheimer's fibrillary changes are typically absent, but, if present in moderate degree, do not exclude the diagnosis of Pick's disease. Changes in the blood-vessels are so insignificant that they cannot be considered as a factor, although Ferraro believes that angiospastic factors may play an important role. Inflammatory changes are absent. No evidence of acute softening is seen. Blood-vessel sprouts are lacking. von Braunmühl (1930) stresses the occurrence of degenerative changes in the extra-pyramidal nuclei. The general systemic examination shows nothing except those changes associated with the intercurrent disease which caused death.

The differential diagnosis is rather difficult and deserves some emphasis. The gradual and rather insiduous character of the mental changes that occur in Pick's disease may resemble certain forms of General Paralysis.

However, negative serological evidence excludes a diagnosis of neurosyphilis. Early in the disease, the exclusion of brain tumour, especially those involving the frontal lobes, may present difficulties. The aphasias, which occur in the second stage, suggest temporal tumour. However, since in Pick's disease there is no increase in intracranial pressure, and the triad of papillœdema, headache, and vomiting is absent, the exclusion of neoplasm should not offer a grave problem. X-ray plates of the skull in Pick's disease often reveal thickening of the vault, whereas, with tumours, thinning and erosions are often present. The encephalographic picture seen in Pick's disease, with the symmetrically dilated ventricles and the abundance of air over the cortex, is conclusive evidence that neoplasm is absent.

Perhaps the most difficult differentiation is between Pick's and Alzheimer's diseases. This cannot be made on any one set of symptoms, but depends more upon the general picture. Pick's disease is more apt to resemble General Paralysis, while Alzheimer's disease tends toward the picture of senile dementia. Confabulation is typically absent in Pick's disease. Memory loss occurs early in Alzheimer's disease, whereas, while it may seem to be impaired in Pick's disease, careful study will reveal that such is not the case, but that, as previously described, use of it as a tool is impaired. Kahn and Thompson consider encephalographic findings to be very helpful in this differentiation. They state that in Alzheimer's disease the subarachnoid air lies in broad, blunted sulci, whereas in Pick's disease it tends to lie in irregular masses. In distinguishing Pick's disease from other forms of dementia, cerebral arteriosclerosis is characterized by the frequent antecedent history of headache, dizziness, and apoplectic phenomena, together with the presence and character of the memory defect and the findings of systemic and retinal sclerosis. Simple senile dementia should not present any difficult problem because of its later age of onset and the character of the memory loss which differs from that in Pick's disease, as has been discussed previously. While in the early stages, the behaviour and emotional reactions might suggest functional mental disease, the organic implications soon become obvious.

CASE REPORT.

Mary S., white, married, aged 56, was admitted to Butler Hospital on January 23, 1933, because of increasing restlessness and personality changes. Family history revealed eccentricity on the part of one maternal cousin, alcoholism in another and mental disease in still another. Birth history and early development were normal. The patient had been a good student, graduated from a business college, and worked as an efficient clerk for nine years prior to her marriage in 1906. In spite of the fact that no contraceptive measures were ever employed, the patient never became pregnant. Catamenia was established at thirteen years, but periods, while regular, were excessive, lasting ten days and accompanied by severe headaches, invariably most marked in the left frontal region. The menopause was completed in 1927 without any disturbing mental or physical symptoms. Concomitant with the menopause, the headaches disappeared. There is no history of abuse of drugs or alcohol. In personality the patient had been lively, friendly, and pleasant, sociable and an active worker, holding several offices in women's clubs. Her mood had been stable and her judgment always considered good.

In retrospect, it seemed that the illness began insidiously in the spring of 1928, at which time the patient was 51 years of age. The first symptoms were irritability, moodiness and periods of mild confusion when hard pressed by her active and varied interests. In the autumn of that year, the patient sustained a small laceration of her scalp in an automobile accident. She was not rendered unconscious, however, nor did she express any physical complaints after the accident. An X-ray of the skull was not taken at that time. The mental changes previously described definitely antedate that accident. From 1928 to 1931 a gradual loss of interest developed, together with deterioration of judgment, and disregard for the ordinary social proprieties. For example, she sent notices of club meetings to outsiders, rather than to the members. At one of the meetings she greeted a long-absent member by saying: " How have you been since your husband's suicide ? " In the discharge of her household duties she had become stereotyped, preparing the same meal day after day until changes were suggested by her husband. Her mood gradually became superficial and her reactions rather childish. During 1932 she showed marked change in the character of her thinking. She initiated very little conversation and began simply to repeat phrases which she heard in the conversations of others. Her mood became progressively more superficial and took on a jocular tone. Gradually there developed a diffuse type of restlessness, which constituted the main problem in her care at home.

Examination on admission revealed the patient to be in good general physical condition. Neurological examination was negative, except for hyperactive, but equal, tendon reflexes. Examinations of all body fluids, including spinal fluid, yielded results which were well within normal limits.

Mental examination revealed her to be alert, pleasant, and co-operative. She giggled freely and her emotional responses in general were superficial. On a few occasions, when things were not exactly to her liking, she rose in fleeting childish indignation. Restlessness was present and of a diffuse, purposeless type, consisting of pacing about the ward and her room, fumbling with newspapers, magazines, flowers and other articles. At times she was noisy, tapping her feet loudly, clapping her hands and slapping her thighs, at no time giving any reason for this behaviour. Her spontaneous speech consisted of superficial, isolated remarks concerning her husband, her home and her telephone number. When questioned, she invariably repeated the question, changing the pronouns from the second to the first person, to suit the occasion. For example, when asked, " How do you feel ? " she replied: " How do I feel ? I feel fine." In her conversation, patient showed a marked restriction of the ideational field. She was unable to give reasoned responses or to elaborate thought material, and, when pressed, made some superficial evasion. The following excerpts from her stream of talk will illustrate these points:—

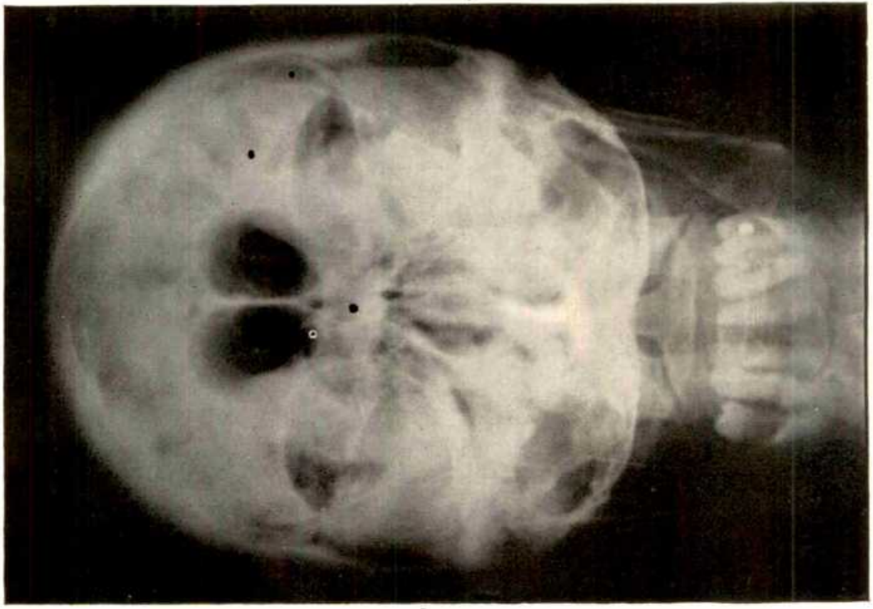
Q.—Did you have a nice breakfast this morning ?

A.—Yes, I had a nice breakfast this morning.

Q.—What kind of cereal did you have this morning ?

A.—What kind of cereal did I have this morning ? I had oatmeal.

PLATE XII



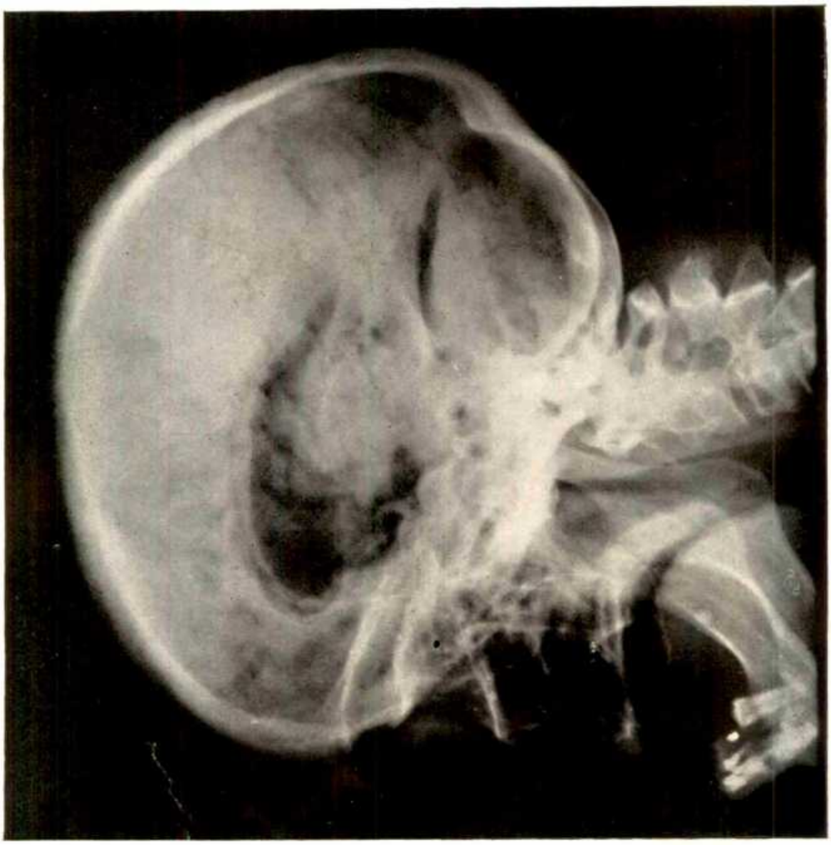


FIG. 1.

To illustrate paper by Ira C. Nichols and Walter C. Weigner.

PLATE XIII.

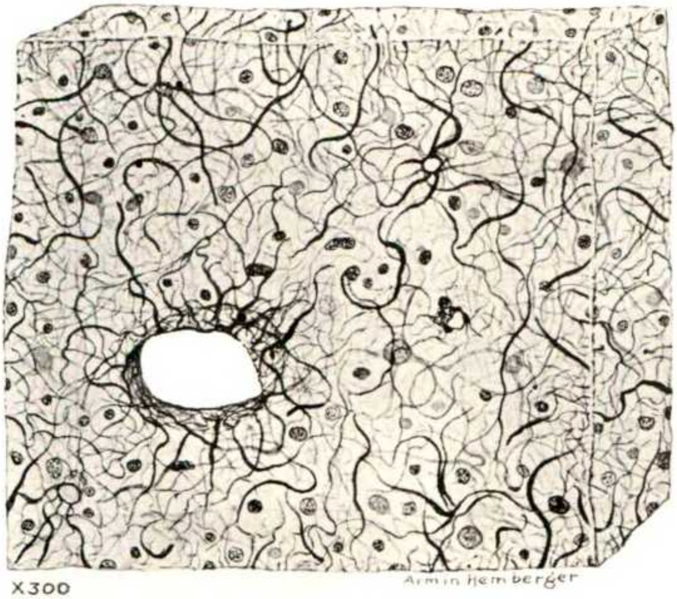


FIG. 4.

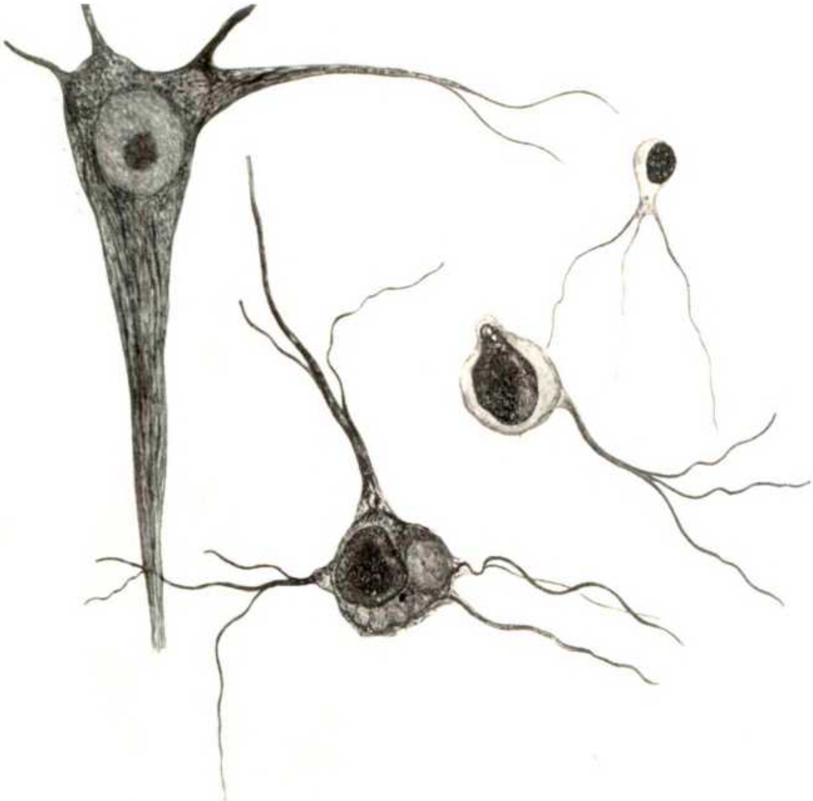


FIG. 5.

To illustrate paper by Ira C. Nichols and Walter C. Weigner.

Q.—Do you like oatmeal ?
A.—Do I like oatmeal? Yes, I like oatmeal.
Q.—Why do you like oatmeal ?
A.—Why do I like oatmeal ? I don't like oatmeal. I like eggs.

She denied hallucinations and there was no evidence of their presence. No delusions were expressed. Memory showed no impairment in either the remote or recent fields ; in fact, memory seemed hyperacute. Her mental grasp was good ; she learned the names of doctors and nurses without difficulty, recognizing them on subsequent visits, and calling them by their proper names. Orientation was intact in all spheres. Insight was absent and judgment was extremely poor.

X-ray plates of the skull[1] revealed no evidence of old or recent fracture, or of increased intracranial pressure. The cranial vault was thickened and there were hyperostoses of the inner table in the frontal region. Encephalograms taken after the introduction of 100 c.cs. of air revealed symmetrical dilatation of both lateral ventricles, more marked in the anterior horns. The 3rd and 4th ventricles were normal. The cortical air pathways were not normally distributed and were dilated four or five times their normal width, indicating considerable cortical atrophy (fig. 1).

With a diagnosis of Pick's disease, the patient was discharged to her home on February 2, 1933. For the following six months she discharged her household duties satisfactorily, except for an increasingly stereotyped character to her daily programme. Gradually her defect of judgment became so marked that it was necessary for her husband practically to take over the management of the home. During the autumn and winter of 1933 and 1934 definite signs of a slowly progressing dementia showed themselves. Memory, which had previously been so acute, began to show minor lapses. Restlessness increased, mood showed further lightening and the ideational field showed gradual further restriction. It was in this stage of the illness that the patient was presented before the Boston Society for Psychiatry and Neurology (1934) Nichols, I. C., and Weigner, W. C., 1934.

Early in 1934 confusion was so great that the problem of wandering away from home necessitated re-admission to the hospital. At the time of this re-admission (February 10, 1934) no change was detected in her physical findings except that the hyperkinesia was more marked than formerly. Although she showed short episodes of confusion, her grasp of her immediate situation was still on the whole surprisingly good. During succeeding months increased untidiness developed to the degree that the patient was incontinent in bed and soiled her clothing. She showed absolutely no insight into this behaviour, simply giggling in a superficial manner when it was brought to her attention. Her previously described echolalic responses continued and, as time went on, it became increasingly more difficult to elicit any answers to questions put to her. Invariably she simply repeated the question in the same form that it had been presented to her. Occasionally she was noisy, chanting simple meaningless phrases at the top of her voice for long periods of time. By December, 1934, restlessness was definitely abating and intellectual faculties were undergoing obvious deterioration. Emotional responses were likewise undergoing change ; whereas formerly she was rather prevailingly euphoric, she was by this time becoming flat in her emotional tone. In June, 1935, abnormal neurological signs were detected for the first time. She had a complete flexor withdrawal on stroking the soles of the feet, or on using the Oppenheim, Chaddock or Gordon manœuvres. Her general health was by this time failing, as indicated by a progressive loss in weight. By the end of 1936 the patient had deteriorated so greatly that she was practically mute. Occasionally she showed some excitement, which consisted in mischievous behaviour, characterized by meddling with other patients' possessions, tipping furniture over, rattling doorknobs, and the like. In the performance of this behaviour she showed great confusion and required almost constant nursing supervision. By the spring of 1937 she had lost a great deal of weight and was readily fatigued. On March 6, 1937, she developed a temperature and signs of pulmonary infection. On the evening of March 13, her temperature rose from 102·8° F. to 109·6° F., at which point she expired. A post-mortem examination was carried out four hours after death. The pathological diagnoses were: (1) Pick's disease (confirmation to be obtained in microscopic sections); (2) bronchial pneumonia, both bases, more marked on the right ; (3) cholelithiasis ; (4) congenital deformity of the left kidney—double ureter ; (5) uterine fibromata ; (6) localized arteriosclerosis: moderate in the arch of the aorta ; marked in the abdominal aorta.

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[1] The authors wish to thank Dr. Isaac Gerber of Providence, Rhode Island, for his assistance in the roentgenological study of this case and for permission to use the plates.

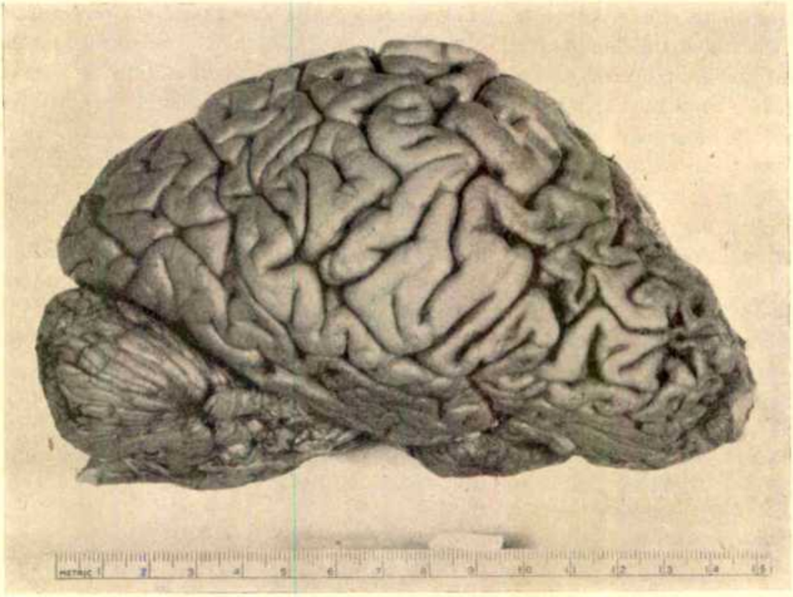

FIG. 2.—View of the right lateral surface. Note the shrunken gyri of the frontal regions which contrast so strikingly with the full-bodied appearance of the gyri in the region of the central sulcus.

Gross and Microscopic Anatomy of the Brain.—The skull appeared thicker and denser than normal. The meninges exhibited no gross abnormality. In the circle of Willis there were only mild atheromatous changes. The brain weight was 950 grm. The brain appeared generally small, but the atrophy in the frontal and temporal lobes was striking. The gyri in these regions were markedly shrunken and exhibiting a brownish discoloration. The sulcii of the atrophic regions were deep, wide, and gaping. On cutting the brain an increased resistance was met. On examining the cut surfaces the normal demarcation between cortex and sub-cortex could not be made out. The anterior horns of both lateral ventricles were dilated but otherwise the system was negative. The basal ganglia and the cerebellum showed no gross evidence of disease (figs. 2 and 3).

On microscopic examination the leptomeninges were normal. The pial and parenchymal vessels were remarkably free of atheromatous changes, except that the arterioles of the corpus striatum and the pallidal nuclei showed considerable calcification. There were, however, no foci of encephalomalacia resulting from these vascular lesions, nor any scars which could be attributed to them.

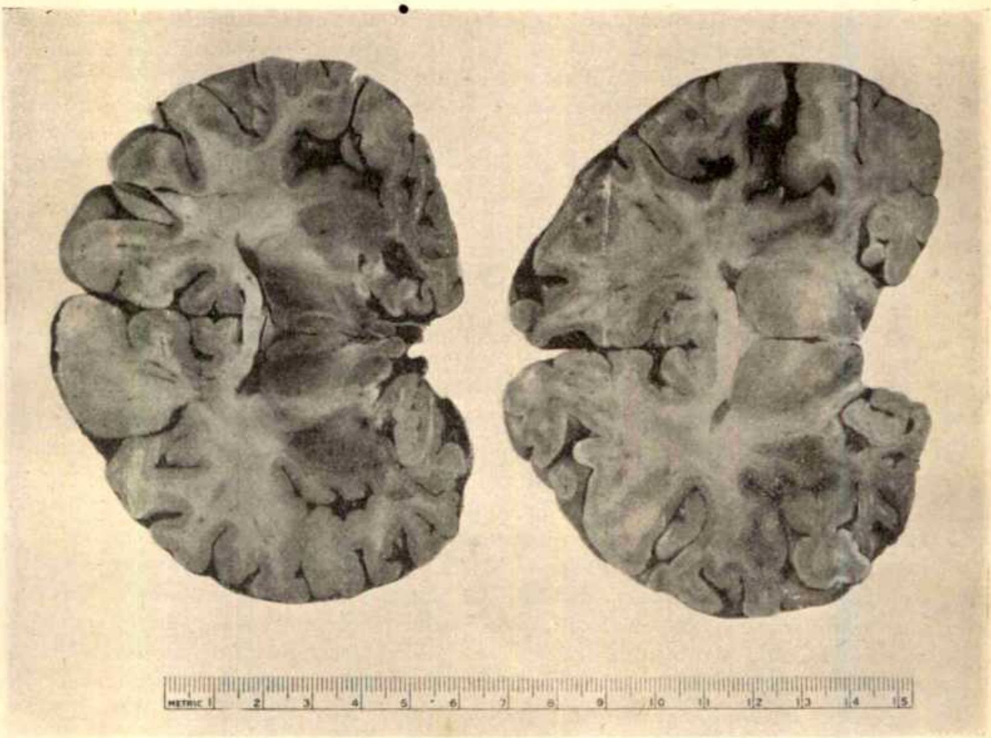

FIG. 3.—Coronal sections showing atrophy which is striking in the gyri of the basal portions of the hemispheres. The normal demarcation between white and gray matter is disturbed especially in the more atrophic gyri.

In the cerebral gyri, which had shown the greatest degree of atrophy macroscopically, the cyto-architecture was profoundly altered. Hardly a single ganglion cell remained in any of the cortical laminæ, yet the cellular population was increased in these layers above normal. The cells, however, were of the glial variety—astrocytes, oligodendroglia and Hortega cells being present in great profusion. There was a conspicuous increase in the marginal glial cells and their processes which were coarse, tortuous and inserted in the membrana limitans (fig. 4). The glial cells and the fibroglial processes were somewhat more scant in the deeper layers where a status spongiosis was frequently in evidence. There was a condensation atrophy of the subcortical white matter in the frontal lobes. Here the oligodendroglial cells were exceedingly numerous and closely spaced, but no actual softening or progressive gliosis was present.

In the less atrophic gyri, such as the insular and cingulate, the microscopic picture was different. Here, only the superficial laminæ were depopulated of nerve cells; the deeper layers still contained their normal or nearly normal quota. But the ganglion cells which remained were strikingly altered. Most of them had become rounded and swollen, their cytoplasm had lost the tigroid markings and had assumed a homogeneous ground-glass appearance. The nuclei of these cells were less distinct and occupied eccentric positions in the cell bodies. In Bielschowsky preparations many of these cells lacked endoneural fibrils and relatively large numbers of them contained the argentophil spheres which are so typical of the histologic picture of Pick's disease. These spheres were usually larger than the nuclei which they displaced to the periphery of the cells. Occasional nerve cells in these less involved portions of the brain were not rounded and swollen at all, but were rather atrophic and hyperchromic (fig. 5).

The caudate nuclei, putamina, pallidal nuclei and substantia nigra were all involved in the atrophic process. In these structures the ganglion cells were slightly decreased in number and some were swollen or atrophic, but there was only moderate glial response. Only the caudate nuclei contained spongy zones. But these central gray structures were altered in another manner, and in this way compare with the cortex. There were enormous deposits of pigment.

Pigment granules were found in great abundance in the cortical and central gray matter and also in the subcortical white matter. In general, the greatest deposits lay in the atrophic portions of the brain. The pigment was of two varieties: one, a coarsely granular brownish material in Nissl preparations and, the other, a more finely granular blue or green material in the same preparations. The latter pigment at least was composed of iron, and this was possibly true also of the former. This pigment was in almost all instances contained in the cell bodies of the various types of glia. In the white matter of the brain the pigment lay exclusively either in the vascular sheaths or in scavenger cells in the perivascular spaces.

Sudan III preparations of the brain contributed much to the histopathological picture of this case. In them there was demonstrable a large amount of lipoidal material within the ganglion cells of the involved portions of the cerebrum. Sudan-staining particles were also found in abundance in the glial cells. Large scavenger cells filled with phagocytosed fat were found in the perivascular spaces of the frontal and temporal lobes, chiefly in the white matter. The large amount of this fat is surprising in view of the relatively negligible extent of the medullary sheath destruction as seen in Kultschitsky preparations. In these, the myelin of the centrum ovale, the corpora striata, the capsulæ extrema (externa and interna), and the pons, medulla and cerebellum were intact. The myelin of the cortex of the frontal and temporal lobes only was degenerated. Here, the cortical radiating fibres were fragmented and ballooned or entirely absent, and the subcortical fibres were poorly stained and appeared frayed or moth-eaten.

The cerebellum, pons, medulla, cervical spinal cord and occipital lobes were unaltered. In the parietal lobes an occasional gyrus was involved. The frontal and temporal lobes suffered most of the injury, and the gyri of the orbital surfaces of the frontal lobes were injured most of all.[1]

SUMMARY.

The dementias occurring during the latter years of life warrant study and clarification. This paper concerns itself with that specific type of dementia which was first described in terms of pathology by Arnold Pick. Although he first considered it as a form of simple senile dementia subsequent observers, adding to his findings, have concluded that it is a specific type of reaction with its own special symptomatology and pathology. Although the diagnosis in most of the reported cases was made post mortem, modern refinements in neuropsychiatric methods now make an earlier diagnosis possible.

Most valuable in our present day armamentarium is a careful psychological study of the memory. In cases of Pick's disease, this reveals a defect which often differs very characteristically from that found in the more usual dementias in that memory itself is not so much disturbed as much as the individual's ability to use it in the formation of new ideational material. It is this "loss of memory as a tool" that careful psychological study brings out. In addition to revealing this specific character to the memory defect, psychological examination also reveals frontal lobe symptoms such as psychical inertia, stereotypy, and disturbances of general and of ethical judgment.

The encephalogram is of great diagnostic value also. Inasmuch as the fundamental pathological process in the disease consists of circumscribed areas of atrophy—an enlargement of the ventricles and pools of subarachnoid air overlaying the atrophic areas are revealed by this method of study.

The course is progressive, leading to a relatively early death, which releases the individual from the vegetative existence of extreme dementia. The chief findings at autopsy are the strikingly circumscribed areas of atrophy which involve chiefly the frontal, temporal, and insular areas and less frequently the occipital and parietal lobes. The diagnostic criteria from the microscopic study are the severe diminution of cells, the intense gliosis, the presence of Pick's cells containing argentophil bodies, and the absence or paucity of senile plaques and Alzheimer's fibrillary degeneration.

A case is reported in which the diagnosis was made by means of the previously mentioned diagnostic procedures four years ante-mortem. The confirmatory post-mortem brain findings are described.

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[1] The authors wish to thank Dr. H. M. Zimmerman of the Laboratory of Pathology, Yale University School of Medicine, New Haven, Connecticut, for his invaluable assistance in the preparation and interpretation of the pathological material.

At the present time it is, of course, unfavourably regarded to call a disease by the name of its discoverer. It is particularly unfortunate in this instance for there is another Pick's disease, a polyserositis, and we also find that Niemann-Pick disease causes confusion. The term circumscribed senile atrophy, which is frequently used, is little better, for this does not separate this condition from other types of atrophy arising from other causes, and the term "senile" hardly suits a disease that may arise early in the forties. The ætiology is not indicated by the name, and since the causation is not definitely known, we believe we should frankly admit our ignorance and use the term idiopathic. In view of the facts to which reference has been made above, we suggest that a more suitable name would be "Idiopathic Circumscribed Presenile Cerebral Atrophy," which compensates for its clumsy length by a great increase in accuracy.

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LEGENDS FOR PLATES.

FIG. 1.—Lateral and anterior-posterior views after introduction of 100 c.c. of air. Note bilateral dilatation of the lateral ventricles extending well anteriorly. In the frontal regions air can be seen lying over the surface in broad irregular masses. In the anterior-posterior view collections of air in the insulæ are clearly shown.

FIG. 4.—Reconstruction of a Victoria blue preparation from the white matter of an atrophic gyrus showing the very rich proliferation of protoplasmic astrocytes. Many of these cells send processes to the walls of the blood-vessel.

FIG. 5.—Reconstruction of cells from a Bielschowsky preparation. Reading from right to left cells are represented in what is probably their progressive order of disintegration. The cell at the extreme right is relatively normal, while the one next to the left is bloated, its nucleus eccentric, and it contains a large argentophil body. The next two cells toward the left are shrunken, their nuclei are lost, and their chief features are the darkly stained argentophil bodies. (× 1,000.)

THE THALAMUS OF THE CHIMPANZEE.[1]

III.—Metathalamus, Normal Structure and Cortical Connections.

BY A. EARL WALKER, M.D.[2] AND J. F. FULTON, M.D.

The differentiated thalamic structures related to the visual and auditory systems in man and monkey have recently been studied intensively (Brouwer, 1936: Clark and Penman, 1934: Poliak, 1933), but the structure and connections of the anthropoid geniculate bodies have been described in only one case (Poliak and Hayashi, 1936). The close resemblance of the ganglia in the anthropoid to those of man, and the possibility of experimentation upon these animals gives particular significance to the study of their structure and relationships.

I.—Normal Structure.

Corpus geniculatum laterale.

The lateral geniculate body of the chimpanzee is similar to that of man and lower primates. It is an inverted, hemispherical, six-layered structure with narrow fibre bands separating the cellular laminæ. The intralaminar fibre zones between the inferior two layers are larger and more distinct than those between the other cellular laminæ. Through the anterior surface of the lateral geniculate body the fibres of the optic nerve enter these fibrous zones and ramify in the cellular layers. The six laminæ of the ganglion vary according to the site of the section. At its anterior and posterior extremities fewer cellular laminæ are present, and at both medial and lateral margins they coalesce forming only three or four distinct layers (fig. 1, Plate XIV).

Histologically, the lateral geniculate body may be divided into three parts, each with characteristic cytology: (i) the dorsal four layers, (ii) the basal two layers, (iii) the *grisea pregeniculata.* The dorsal four cellular laminæ are composed of uniform, medium-sized neurons fairly compactly arranged. The cells are oval or circular in shape and clearly outlined, although a cell membrane can not be distinguished. The hyaloplasm stains diffusely in Nissl preparations. The dendrites are unstained although occasionally the axon hillock may be recognized. Numerous small and large chromatic granules are scattered throughout the cell. The pale-staining nucleus is well outlined by a distinct nuclear membrane. It is usually two-thirds the width of the cell. Numerous fine trabeculæ traverse the nucleus, many passing to the circular, diffusely staining nucleolus Satellitosis is uncommon, most of the neurons being devoid of glia or have only one glial cell. Scattered among the cells of this type are smaller, paler staining neurons comprising 10 to 15 per cent. of the total cellular mass.

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[1] From the Laboratory of Physiology, Yale University School of Medicine, New Haven, Connecticut. This work was aided by a grant from the Research Funds, Yale University School of Medicine.

[2] Fellow of the Rockefeller Foundation, 1935-36, now of the Division of Neurology and Neurosurgery, University of Chicago, Chicago, Illinois.

The histological appearance of the neurons in the two basal layers of the lateral geniculate body is similar to that of the upper four laminæ, except that the cells are slightly larger, and less compactly arranged, the hyaloplasm more densely staining and the Nissl granules coarser.

Lying along the anterior surface of the dorsal portion of the lateral geniculate body is a loosely arranged collection of cells representing the *grisea pregeniculata.* The cells of this nuclear mass are slightly larger than those of the dorsal layers of the geniculate body, and polygonal or angular in shape. The hyaloplasm stains lightly so that the Nissl substance stands out clearly. The axon and dendrites of the neuron stain lightly giving a distinctly angular appearance to the cell. Satellitosis is the rule, two to four glial cells surrounding each neuron. The intensely staining nucleolus stands out prominently within the pale nucleus.

Corpus geniculatum mediale.

The medial geniculate body is an irregular mass of cells situated laterally between the inferior nucleus of the pulvinar and the lateral geniculate body, and the pes pedunculi medially. It is absolutely, but probably not relatively, increased in size, over its comparable structure in the macaque and lower primates. Its magnocellular division is smaller than that in the lower primates and its main portion is larger. At its rostral extremity large cells are widely dispersed so that the division between the two parts of the nucleus is difficult to distinguish. The relationships of the medial geniculate body are much the same as in the lower primates. Lateral to it is the nucleus pulvinaris inferior and the corpus geniculatum mediale, medially the nucleus peripeduncular and anterior tegmental nuclei and superiorly the nucleus suprageniculatus and ventral thalamic nucleus. With the exception of the nucleus suprageniculatus, which merges almost imperceptibly with the magnocellular portion of the medial geniculate body, the boundaries of the nucleus cause no confusion. The nucleus suprageniculatus is situated anteromedially and is composed of dark staining, scattered cells, which are readily recognized in the normal specimen but may cause confusion in an area distorted by atrophy and gliosis (fig. 1, Plate XIV).

The main portion of the nucleus is composed of uniformly arranged, medium-sized, ovoid cells with large pale nuclei. The nucleus, occupying almost half the cell, is usually found at one end. The nucleolus is a prominent structure in the pale staining nucleus. Scattered irregularly through the lightly staining cell hyaloplasm are clumps of Nissl substance. Many neurons have one or two satellite glial cells. The magnocellular portion of the medial geniculate body consists of larger, more rounded but less compactly arranged, neurons. The hyaloplasm stains diffusely and more intensely; the Nissl substance is more prominent but regularly arranged in the cell. Although most of the neurons of the medial geniculate body are of these types, a few smaller, and paler staining cells are encountered.

Experimental Methods.

The animals used in this investigation were immature chimpanzees (*Pan satyrus*) which had been under observation for some time in the laboratory. General anæsthesia and complete surgical asepsis was used for all operative procedures. Both animals to be described lived more than six weeks after the final operative procedure. They were sacrificed under deep ether anæsthesia and the vascular system perfused immediately after death with saline followed by 95 per cent. alcohol. The thalami were quickly removed by blunt dissection in order to obtain optimal fixation. After hardening in 95 per cent. alcohol, the hemispheres were photographed, the lesions examined and minutely described. The lesions accompanied by a generous amount of surrounding cortex, were then further fixed in 95 per cent. alcohol and ether, and embedded in celloidin. Coronal serial sections were made of both the cortex and thalami. Every 25th section of the cortex was cut at 25 microns and stained by Nissl's thionin method. In one animal every third (Snookums) and in the other every fifth (Ghandi) section of the thalamus was stained by the same technique and mounted. All illustrations were made from direct projection of the sections. The lesions and degenerations (solid black or heavy stippling in the illustrations) were filled from direct microscopic examination of the sections. The number under each drawing indicates the section from which the drawing was made.

The following abbreviations have been used in the illustrations:—

CF.	fissura calcarina.
IH.	cornua inferiore, ventriculi cerebri.
IS.	sulcus intraparietalis.
L.	lateral.
M.	medial.
OD.	sulcus occipitalis diagonalis.
PE.	sulcus parieto-occipitalis externa.
PI.	sulcus parieto-occipitalis interna.
SS.	sulcus sylvii.
ST.	sulcus temporalis superior (parallel sulcus).

II.—Experimental Results.

In a previous study (Walker, in press), it has been found that in the chimpanzee after hemidecortication, the lateral geniculate body is virtually devoid of normal cells. Occasional cell shadows and shrunken cells were present especially in the lower two layers. The medial geniculate body, including its magnocellular portion, was found completely degenerated except for an occasional normal appearing cell. Its adjacent suprageniculate nucleus was entirely spared, as were also the cells along the lateral portion of the cerebral peduncles and the *grisea pregeniculata.* It may, therefore, be assumed that practically the entire medial and lateral geniculate bodies project to the cerebral cortex. Details of this projection have been determined in the following two experiments.

Experiment 1.—Lesion of right occipital pole; degeneration of medial portion of the lateral geniculate body. Ablation of left occipital lobe and small lesion of the superior temporal convolution; severe degeneration of the left lateral and medial geniculate bodies. Weight 11·3 kg. (Snookums).

The subject of this experiment was a timid, temperamental young female chimpanzee, in excellent condition except for a desquamating dermatitis over the head and neck. On February 19, 1936, a right osteoplastic craniotomy was performed. The inferior half of the post-central convolution and the occipital operculum juxtaposed to the external parieto-occipital fissure were ablated. On April 2, 1936, a left osteoplastic craniotomy was performed exposing the occipital and posterior temporal regions. The left occipital lobe posterior to the parieto-occipital fissure was removed in one piece. The Sylvian fissure was opened and with a brain spatula the cortex lying on a small ridge on the superior surface of the first temporal gyrus was removed by subpial dissection. The neurological disturbances resulting from these ablations will be described in another connection. The visual disturbances were similar to those described by Spence and Fulton (1936). On May 28, 1936, the animal was sacrificed.

Anatomical Examination.

Right cerebral hemisphere.—The sites of two cortical lesions are as follows: One occupies the inferior two-thirds of the post-central convolution, and the second the rostral portion of the lateral surface of the occipital lobe, extending parallel with the parieto-occipital sulcus. It begins 1 cm. from the mid-line as a lesion 0·6 to 0·7 cm. in width tapering inferiorly to its termination just above the tip of the sulcus occipitalis diagonalis.

Serial sections of the occipital lobe confirm the gross location of the lesion. Its posterior margin borders upon striate cortex. The anterior margin on the posterior wall of the external parieto-occipital sulcus is bounded mainly by cortex of type 18 and in a few places by type 19. In the lower part of the lesion there is slight involvement of the annectant cortex of the posterior parietal lobe but the greater part of the apparent damage is the result of accidental hæmorrhage at the time of sacrifice, considerable fresh blood being present in the parieto-occipital sulcus and a small amount in the tissues of the cortex anterior to the external parieto-occipital sulcus.

There is, however, a small old superficial lesion of the anterior lip of this sulcus. In no place does the main lesion extend into the cortex for more than 1 to 2 mm. (fig. 2).

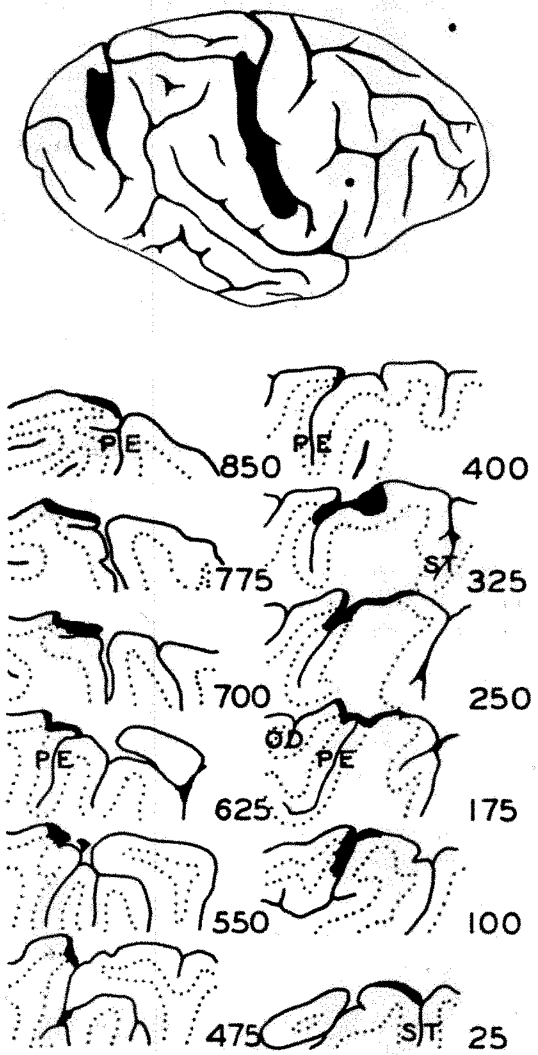

FIG. 2.—The right cerebral hemisphere of chimpanzee Snookums and sketches of serial sections of the occipital opercular lesion.

Right lateral geniculate body.—An examination of serial sections of the thalamus reveals a zone of retrograde cell degeneration along the medial aspect in the posterior half of the lateral geniculate body. The degeneration, involving all six layers, first appears along the extreme medial margin of the nucleus a few sections from the caudal pole. Anteriorly, it enlarges but maintains its medial and peripheral position through the posterior quarter of the nucleus. At this level a narrow zone of normal

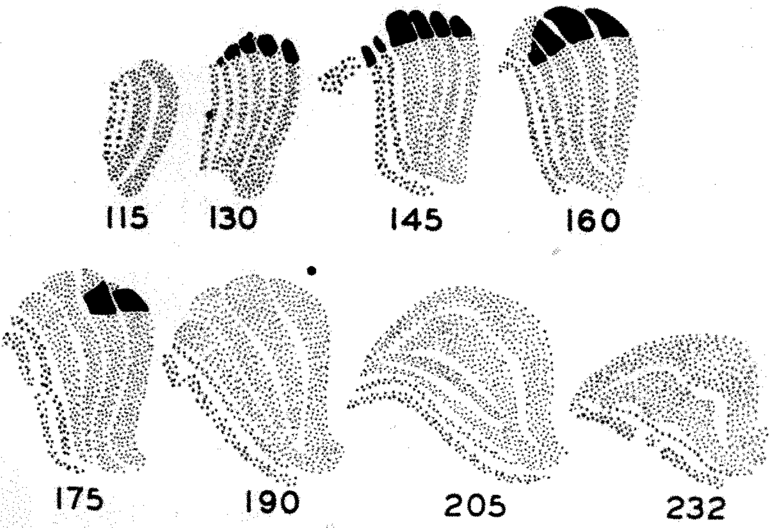

FIG. 3.—Representative serial sections of the right lateral geniculate body of chimpanzee Snookums showing the extent of the retrograde cell degeneration.

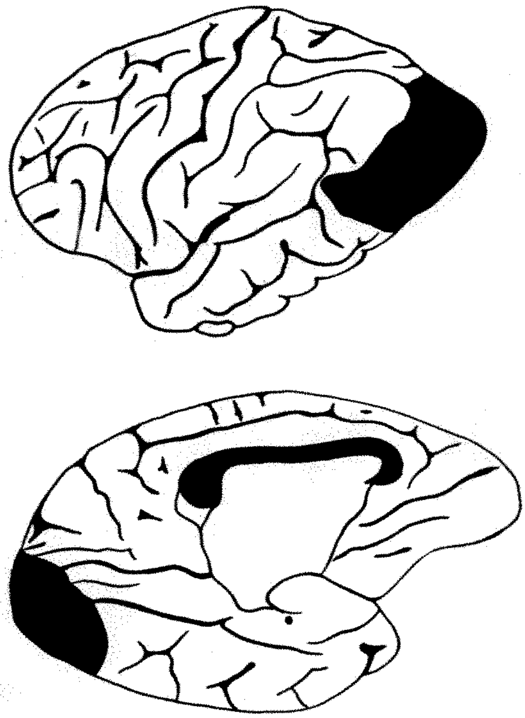

FIG. 4.—The left cerebral hemisphere of chimpanzee Snookums to show the site and extent of the cortical lesions.

cells appears medial to the degenerated area which becomes confined, slightly further anteriorly, to the outer layers of the geniculate body. The degeneration gradually decreases and at the middle of the lateral geniculate body disappears (fig. 3).

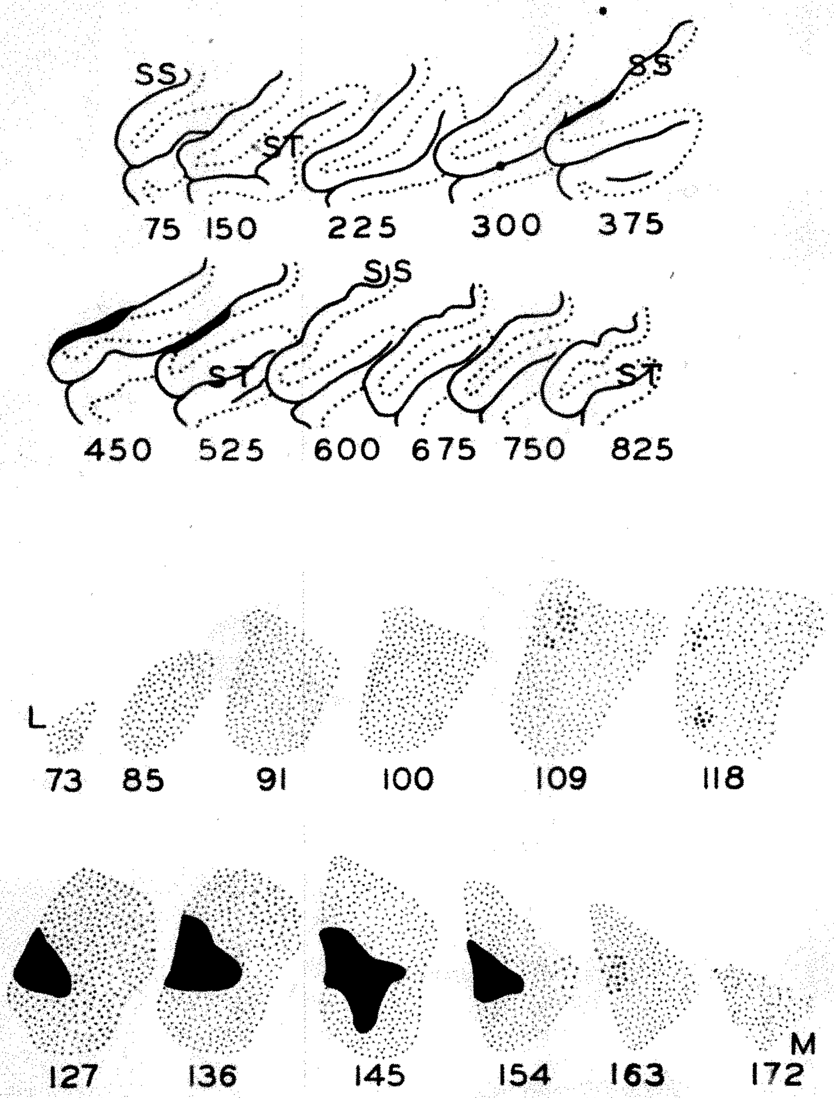

FIG. 5.—Sketches of serial sections of the left Sylvian region of chimpanzee Snookums to show the extent of the lesion, and (below) the retrograde cell degeneration in the medial geniculate body.

Left cerebral hemisphere.—Two lesions are visible in the left cerebral hemisphere (fig. 4). Immediately below the tip of the inferior post-central sulcus a linear injury 0·8 cm. in length lies along the superior margin of the first temporal convolution, but does not involve the cortex on the convexity of the gyrus. Serial sections of the left temporal lobe show a superficial lesion entirely confined to the concealed intra-Sylvian portion of the superior temporal convolution. Laterally the lesion is bounded by Area 22 cortex, but medially and posteriorly by "koniocortex" (*see* Beck, 1938). The margin anteriorly is in temporal cortex of a transitional type (fig. 5).

The second lesion is an ablation of the occipital lobe posterior to the parieto-occipital fissure. The cortex on the anterior wall of this sulcus has been damaged in varying degrees. Inferiorly a superficial lesion extends almost to the posterior margin of the superior temporal sulcus. Superiorly the annectant gyri are injured but the superior parietal lobule is undamaged. The cuneus on the medial surface of the hemisphere is intact except for the ablated superior lip of the calcarine fissure. On the inferior surface of the occipital lobe the damage is more extensive than that on the medial surface of the hemisphere.

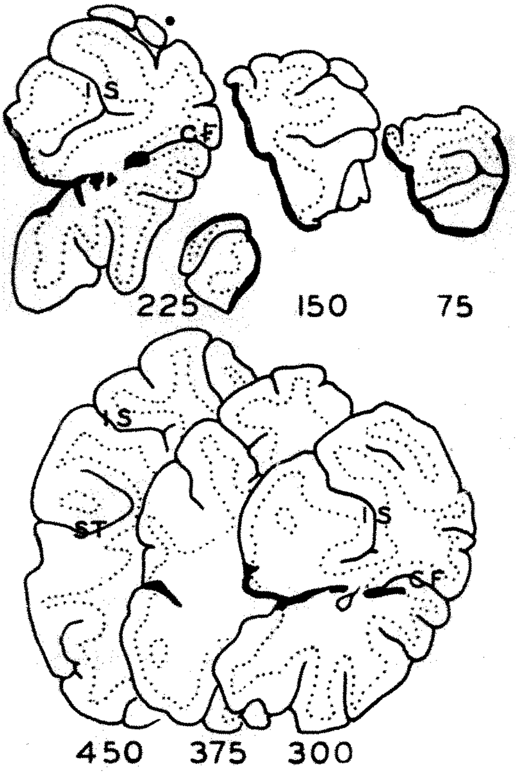

Fig. 6.—Serial sections of the left occipital lobe of chimpanzee Snookums to show the extent of the cortical lesion.

Serial sections of the occipital lobe show that the striate cortex of the lateral surface has been ablated, but along the anterior margin of the calcarine fissure within its depths a small strip is preserved on both lips. Somewhat more striate cortex is present on the superior than on the inferior lip of the calcarine fissure. Area 18 bounds the lesion about the depth of the parieto-occipital fissure, but the greater part is bounded by cortex of Area 19. The lesion on the lateral surface of the hemisphere has this type of cortex on its margins except in the angular gyrus where Area 22 and Area 7 bound it (fig. 6).

Lateral geniculate body left.—Serial sections show that the left lateral geniculate body is severely changed. Its entire posterior pole is completely degenerated, but at about the posterior quarter of the nucleus a narrow zone of normal cells in all six layers appears on its inferolateral margin. The entire posterior half of the dorsal and medial portions of the geniculate body is completely degenerated. At approximately the middle of the lateral geniculate body a zone of normal cells appears along its medial portion giving the degenerated portion a wedge shape. Anteriorly the degenerated area becomes smaller and smaller but constantly maintains its central position almost to the anterior pole of the medial geniculate body (fig. 7).

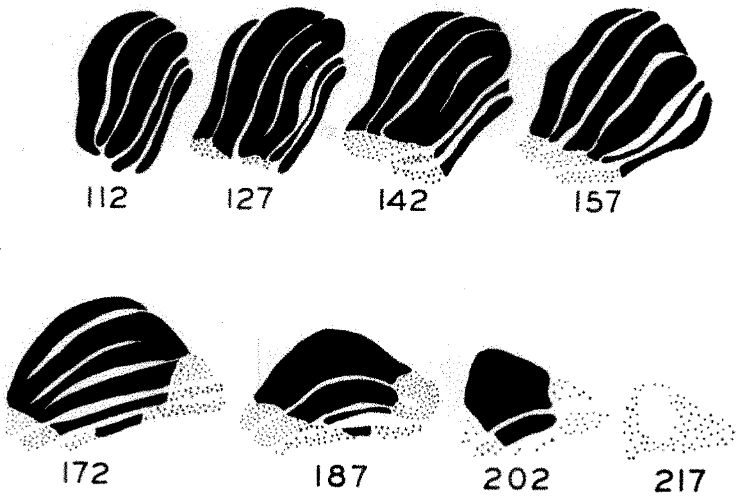

FIG. 7.—Representative serial sections of the left lateral geniculate body of chimpanzee Snookums to show the extent of the retrograde cell degeneration.

Left medial geniculate body.—There is but one zone of degeneration in the left medial geniculate body extending along the lateral surface in its anterior half. Near the posterior pole it commences as a small area of cellular degeneration in the dorsolateral portion of the medial geniculate body. This enlarges and coalesces with a smaller area which becomes apparent slightly more inferiorly, forming a well-defined area of complete cellular degeneration along the lateral margin. It is situated in the mid portion of the nucleus, ventrodorsal. Anteriorly the degeneration maintains its topographical position with slight changes in shape to near the rostral pole of the medial geniculate body. At this level the degeneration becomes scattered and disappears (fig. 5).

Experiment 2.—Linear incision in left superior striate cortex; degeneration in medial portion of the left lateral geniculate body. Ablation of first and second temporal convolutions on right severe degeneration of medial and lateral geniculate bodies. Weight 22·1 kg. (Ghandi).

The subject of this experiment was an immature but well-adjusted male chimpanzee. At the first operation, November 8, 1935, lesions were made in the left motor leg area and superficially in the left supramarginal gyrus. On December 4, 1935, under sodium amytal anæsthesia a low right temporal craniotomy was performed with the assistance of Dr. E. H. Botterell. The first and second temporal convolutions from the tip of the temporal lobe to the inferior margin of the angular and supramarginal gyri were removed *en bloc*. Convalescence was uneventful. A third operation was performed on January 13, 1936, when the left premotor leg area was removed and linear incisions made in the post-central convolution. On February 18, 1936, under ether anæsthesia a small linear incision was made through a burr hole in the medial surface of the left occipital lobe. The animal was sacrificed April 3, 1936.

Anatomical examination.

All lesions were sectioned serially so that the precise extent of the injuries could be accurately ascertained. There were no subcortical softenings in the left hemisphere, and, since the lesion of the supramarginal gyrus was quite superficial, it seems fair to assume that it did not interrupt the visual radiation.

Right cerebral hemisphere is the site of a lesion occupying the first and second temporal convolutions extending from the tip of the temporal lobe posteriorly for 3 cm. and inferiorly from the Sylvian fissure and the cortex of the island of Reil both of which appear undamaged. Posteriorly a part of the superior temporal convolution remains and the margin of the lesion slopes inferiorly to the middle temporal sulcus. This sulcus forms the greater part of the inferior margin of the ablation. Anteriorly a small part of the tip of the temporal lobe remains.

Serial sections of the temporal lobe confirm the gross location of the lesion. Its superior margin follows the lower angle of the Sylvian fissure from almost the tip of the temporal lobe to the posterior margin of the insula sparing entirely the cortex of the latter. At this point on the inferior lip of the Sylvian sulcus, cortex of the granular type (" koniocortex ") bounds the lesion. The latter rapidly becomes superficial, thus completely sparing the posterior and medial portions of the auditory " koniocortex." The lower border of the lesion along the inferior temporal convolution is bounded by cortex of Area 20. Near the posterior extremity of the lesion cortex of Area 21 appears. The lesion extends deeply into the substance of the temporal lobe but a narrow margin of white matter surrounds the lateral surface of the inferior horn of the lateral ventricle. There is no evidence of direct damage to the striate cortex in any part of the lesion. In fact there is no striate cortex in any section of the cortex cut well posterior to the lesion. The anterior two-thirds of the first and second temporal convolutions have thus been largely ablation, i.e. Areas 22, 21, and auditory " koniocortex " (fig. 8).

Right lateral geniculate body.—Serial sections reveal marked degeneration in the lateral part of the anterior half of the lateral geniculate body. At approximately the rostral extremity of its posterior quarter scattered degeneration is present at its lateral margin. Anteriorly this area increases in extent. In the degenerated areas, however, a few normal cells always remain, a condition which is quite unlike the degeneration produced by damage of the striate cortex itself. In the anterior half of the lateral geniculate body, the changes become more intense and its margin is completely degenerated. An intermediate zone between the completely degenerated and the normal exists in which only scattered degeneration is present. The medial half is normal throughout (fig. 9).

Right medial geniculate body.—Serial sections of the medial geniculate body show marked degeneration with severe gliosis in its entire inferior portion. A zone of degeneration in the inferior fourth of the medial geniculate body extends from the posterior pole to the middle of the nucleus. At this level a narrow layer of

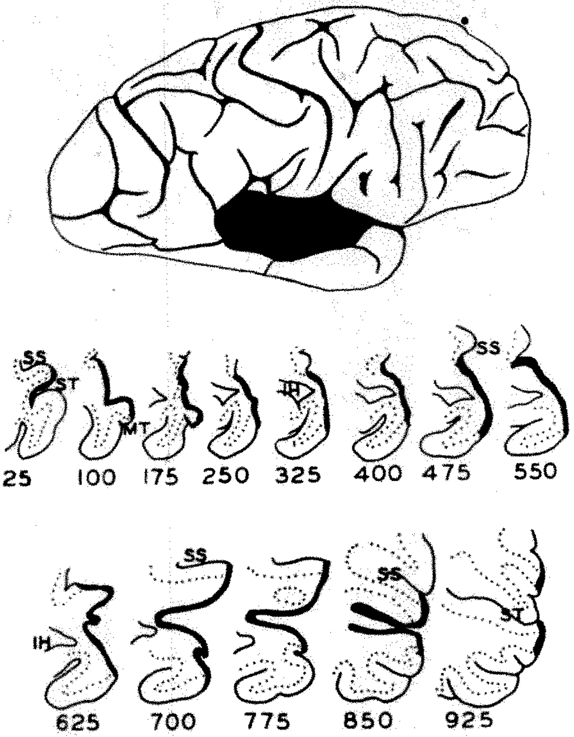

Fig. 8.—The right cerebral hemisphere of chimpanzee Ghandi showing the extent of the temporal ablation and serial sections of the lesion to show its precise limits.

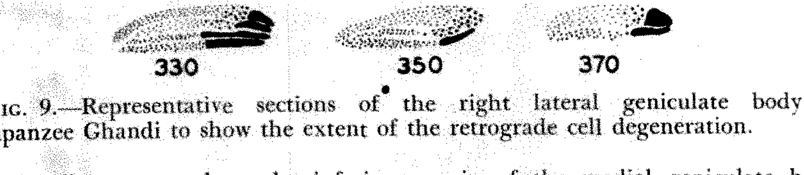

Fig. 9.—Representative sections of the right lateral geniculate body of chimpanzee Ghandi to show the extent of the retrograde cell degeneration.

normal cells appears along the inferior margin of the medial geniculate body. Further anteriorly this layer increases in thickness so that the degenerated zone extends as a transverse band across the medial geniculate body. At the oral

PLATE XIV.

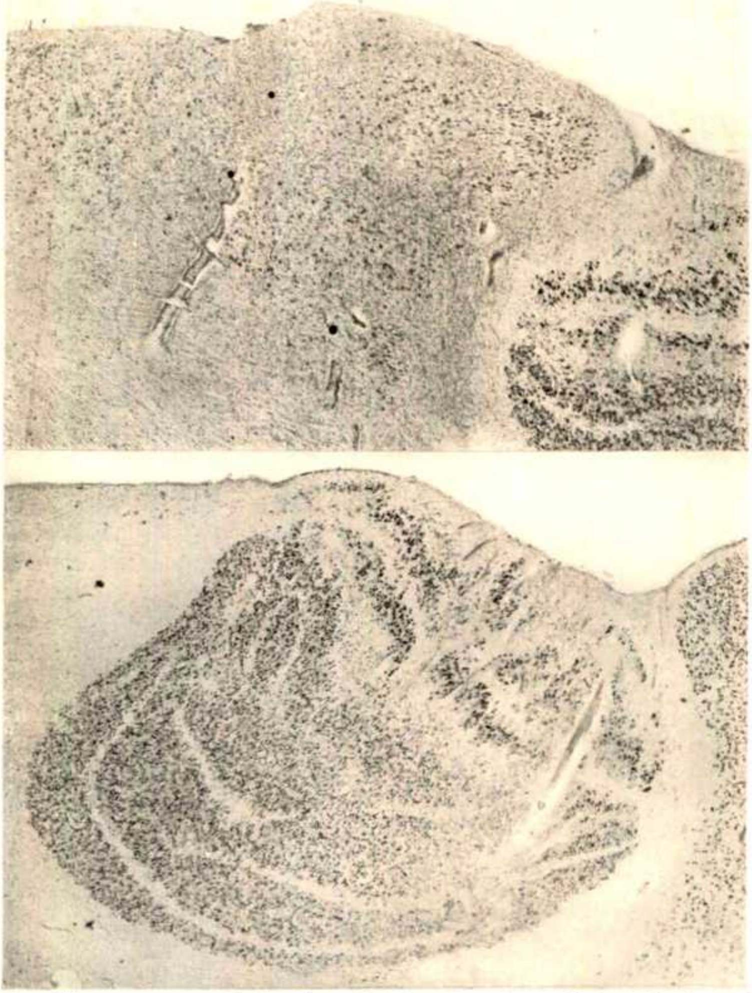

FIG. 1.—The structure of the lateral (above) and medial (below) geniculate bodies. In the lateral geniculate body (chimpanzee Ghandi, left section 260) is an area of retrograde cell degeneration involving the outer four layers. A horizontal layer of cellular degeneration is present in the medial geniculate body (chimpanzee Ghandi, right section 255).

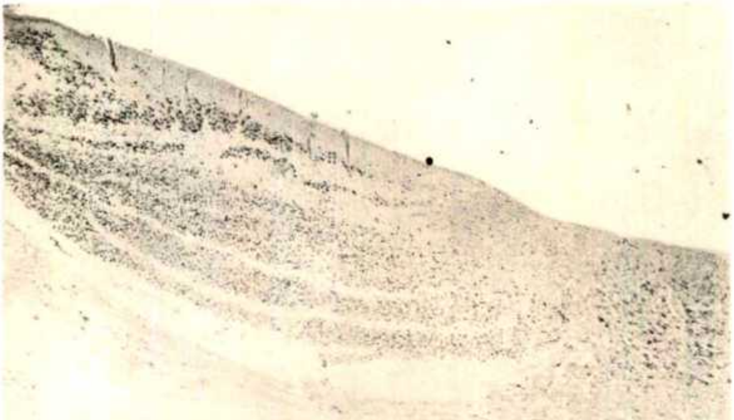

FIG. 10.—Photomicrograph of the right geniculate body of chimpanzee Ghandi (section 300) to show the type of cellular degeneration (compare with fig. 1).

To illustrate article by A. Earl Walker and J. F. Fulton extremity of the nucleus the changes are less intense and normal cells are interspersed in the degenerated area (fig. 11).

Left cerebral hemisphere.— A linear incision lies just posterior to the external parieto-occipital sulcus parallel to the longitudinal fissure. It measures 0·6 cm. in length and is 0·3 cm. from the mid-line. Serial sections of this block from the medial surface of the left occipital lobe show that the lesion pierces just behind the anterior margin of the striate cortex and penetrates to the posterior branch of the internal parieto-occipital sulcus. It lies slightly in front of the anterior branch of the calcarine fissure just touching the striate cortex on its anterior margin. The cortex on the inferior wall of the internal parieto-occipital fissure is only slightly damaged

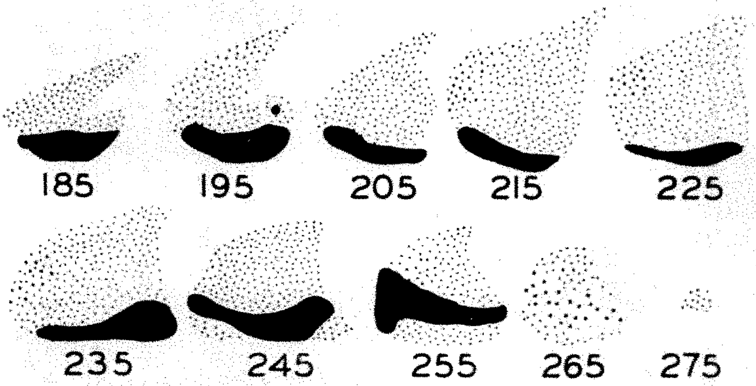

Fig. 11.—Serial sections of the right medial geniculate body of chimpanzee Ghandi to show the extent of the retrograde cell degeneration.

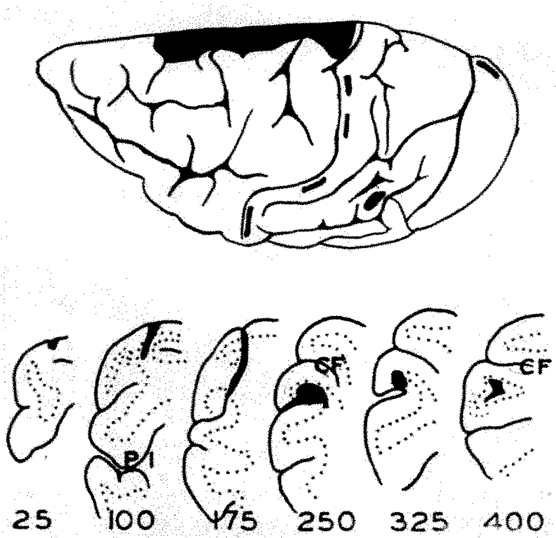

Fig. 12.—The left hemisphere of chimpanzee Ghandi showing the site of the cortical lesions, and (below) representative serial sections of the occipital lobe lesion to show its precise extent.

(fig. 12). The lesions of the left pre- and post-central convolutions of this animal are described in another paper of this series (Walker, in press.).

Left lateral geniculate body.— Careful examination of the serial sections reveals degeneration only in the middle third of the left lateral geniculate body. Approximately at the oral extremity of its posterior third, degeneration appears in the outer three or four layers along the medial border of the geniculate body. Anteriorly this zone enlarges but becomes slightly more laterally situated, a small portion of the normal lateral geniculate body appearing along the medial border. At this point the zone of wedge-shaped degeneration involves the outer five layers of the geniculate body. Further anteriorly it decreases in size and is confined to the second layer. At its anterior extremity, slightly oral to the middle of the lateral geniculate body, it involves only the second layer (fig. 13).

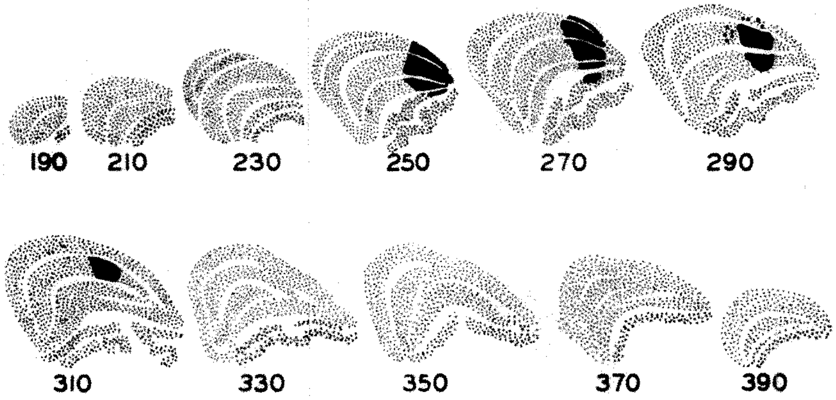

FIG. 13.—Representative serial sections of the left lateral geniculate body of chimpanzee Ghandi showing the extent of the retrograde cell degeneration.

III.—DISCUSSION.

Cortical projection of the lateral geniculate body.

The cortical receptive area for the visual radiation has been known for many years. Indeed, the unique characteristics of the striate region first directed the attention of histologists to the differences in the minute structure of the cerebral cortex. When the significance of cytoarchitectonics was still a matter of speculation, investigators suggested that the striate region was the seat of cortical representation of visual activity. But it required years of investigation by numerous workers to prove this thesis. Further clinical and experimental studies were necessary to determine the arrangement of the visual projection upon the striate cortex. For this information we are largely indebted to Henschen (1924), Gordon Holmes (1918), Brouwer (1936) and others and to the confirmatory studies of Brouwer and Zeeman (1935), Poliak (1932, 1933) and Le Gros Clark and Penman (1934).

The results of the present investigations supplement these previous studies. It may be assumed on the basis of clinical cases and experimental studies of Spence and Fulton (1936) in the chimpanzee that the posterior pole and lateral surface of the striate cortex represents the macular cortex. In the present research two lesions in this region were studied, both in the upper half of the occipital pole. The first (Experiment 1, right cerebral hemisphere) lies along the posterior margin of the striate cortex and has given rise to degeneration in the medial and posterior part of the lateral geniculate body. The second (Experiment 2, left hemisphere) is located slightly more anteriorly on the margin of the striate area and the resulting degeneration is along the medial margin of the lateral geniculate body but slightly more anteriorly placed.

From these two experiments certain general deductions may be made concerning the arrangements of the visual projection to the striate area. That both lesions were above the calcarine fissure and the degenerations in both cases were in the medial portion of the lateral geniculate body is in accord with the previous findings in both man and animals, i.e., *the medial half of the lateral geniculate body projects to the upper lip of the calcarine fissure.* The second deduction concerns the arrangement of the visual radiation. Both lesions damaged the margin of the striate cortex, and produced retrograde cell degeneration along the medial corner of the lateral geniculate body. This favours the suggestion that the borders of the striate cortex receive their afferent fibres from the margins of the medial geniculate body, and conversely that the cortex on the trough of the calcarine fissure derives its afferent geniculate fibres from the middle portions of that nucleus. Moreover, the lesion at the caudal pole of the striate area gave rise to degeneration more posteriorly than the lesion slightly more anteriorly placed. This observation indicates that the more posterior parts of the lateral geniculate body tend to project to the posterior parts of the striate cortex. This spatial relation is further clarified by a comparison of the degeneration in the lateral geniculate body of Experiment 1 with the changes in the same nucleus in Poliak and Hayashi's (1936) chimpanzee, which suffered a less extensive occipital lobectomy (more striate cortex being spared along the anterior portion of the calcarine fissure). The degeneration in this animal does not extend as far anteriorly in the lateral geniculate body as that in Experiment 1 of this study, and the degenerated sectors at each level are smaller.

With this information it is possible to illustrate schematically the projection of the lateral geniculate body upon the striate cortex of the occipital lobe (fig. 14). In this diagram the retinal projection upon the medial geniculate body and the striate cortex has been included by reference to the work of Gordon Holmes (1918), Brouwer (1936), and Le Gros Clark and Penman (1934). It is apparent from this diagram that a lesion along the upper or lower margin of the striate cortex would cause retrograde cell degeneration in the medial or lateral portion of the lateral geniculate body. It is also evident that the more anterior parts of the lateral geniculate body send their fibres to the more anterior portions of the striate cortex. The

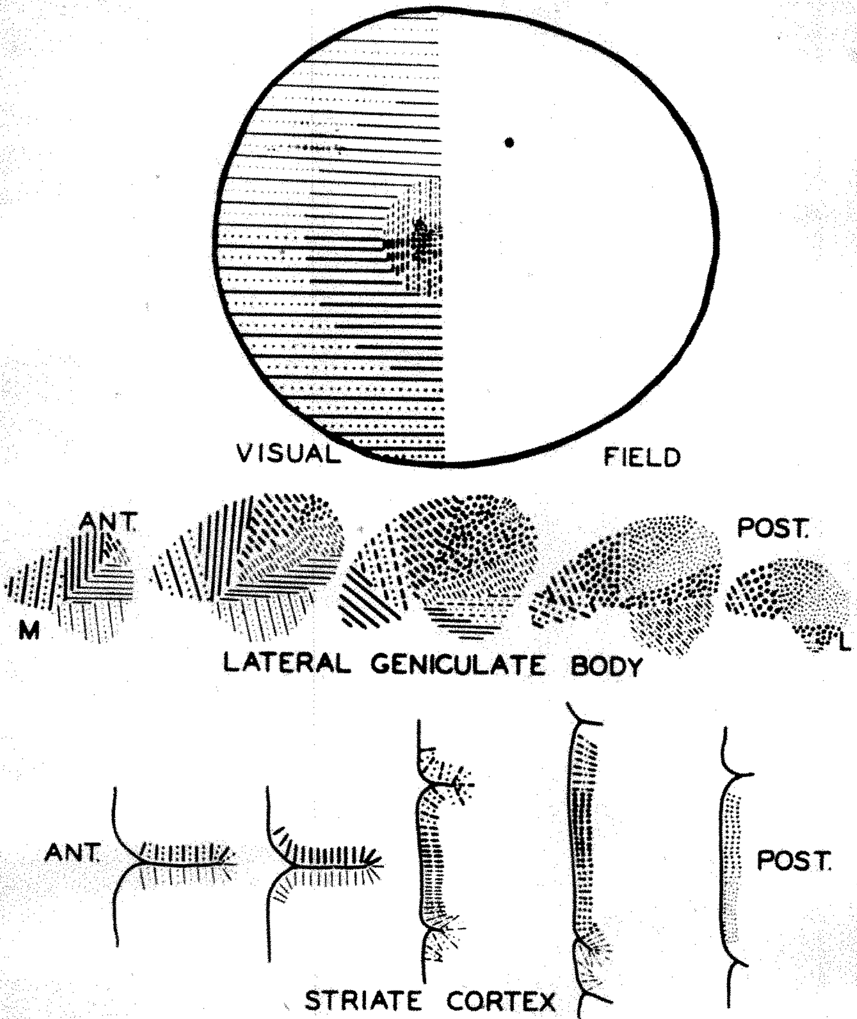

FIG. 14.—A schema to show the projection of the lateral geniculate body upon the striate cortex as determined by this investigation, and the retinal projection upon the lateral geniculate body and striate cortex on the basis of previous investigations.

manner of "figure" projection described by Poliak becomes apparent from this schema.

The degeneration in the lateral geniculate body following a large temporal lobe ablation would be difficult to understand if the path of the visual radiation were unknown. But many clinical observations have shown that the course of the geniculostriate fibres is through the temporal lobe. The site of degeneration in the lateral geniculate body following the temporal lobe ablation corresponds with portion of the nucleus projecting to the inferior lip of the anterior part of the calcarine fissure. Involvement of this portion of the visual radiation would be expected to give rise to a superior quadratic defect in the visual field. Clinically Bailey (1933) and many others have shown that such a defect is a common occurrence with tumours of the temporal lobe. Actually the degeneration in the lateral geniculate body in Experiment 2 following the temporal lobe lesion was quite different from that following an occipital lobe injury (compare fig. 1 and fig. 9). The patchy degeneration of the lateral geniculate body in the first instance probably indicates that the component parts of the visual radiation do not maintain an exact constant relationship throughout their course, and that there is some intermingling of the fibres.

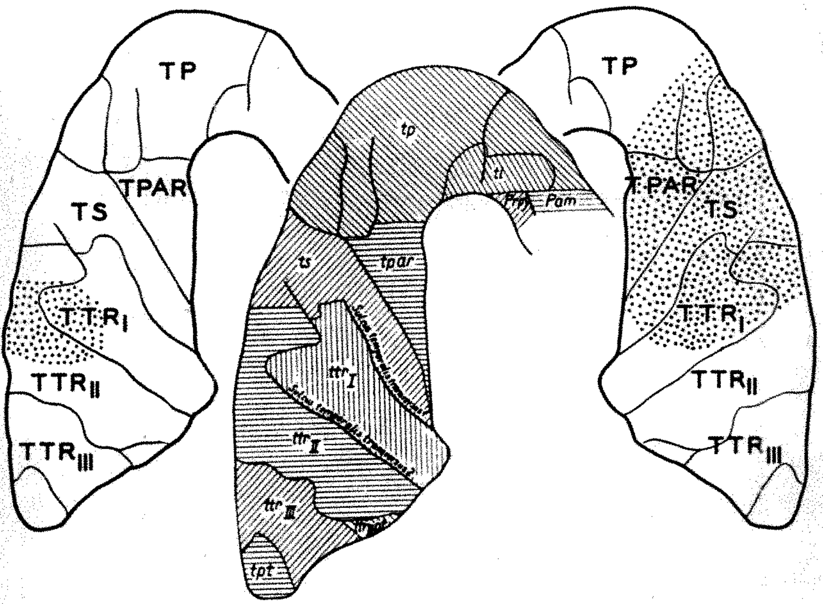

FIG. 15.—The myeloarchitectural fields of the Sylvian region in the chimpanzee after Beck, and the present lesions plotted on this areal map. At the left the lesion in Experiment 1 and at the right that of Experiment 2.

Cortical projection of the medial geniculate body.

In spite of much investigation, the central auditory radiation is not clearly understood. That the temporal cortex is the central representation of the auditory system has been generally accepted for many years. Histological studies of the cytoarchitecture of this part of the brain led Campbell (1905), Brodmann (1909), von Economo and Beck to the conclusion that the transverse temporal convolution of Heschl was the primary auditory centre. The early investigators were unable to describe comparable receptive zones in the lower primates and carnivora, although recently Beck (1938) has suggested that such a cytoarchitectural area probably is present in the monkey. Poliak (1932) inclined to the same idea from his experimental studies. Walker (1937) has described an area of auditory "koniocortex" in the macaque monkey limited to the superior surface of the first temporal convolution. For the chimpanzee Beck has described in detail the myeloarchitectural structure of the Sylvian region (fig. 15). The first transverse temporal convolution in this animal is rudimentary, and Beck believes that the central auditory projection area is not confined to it but extends further posteriorly (including TTR I, TTR II, and TTR III).

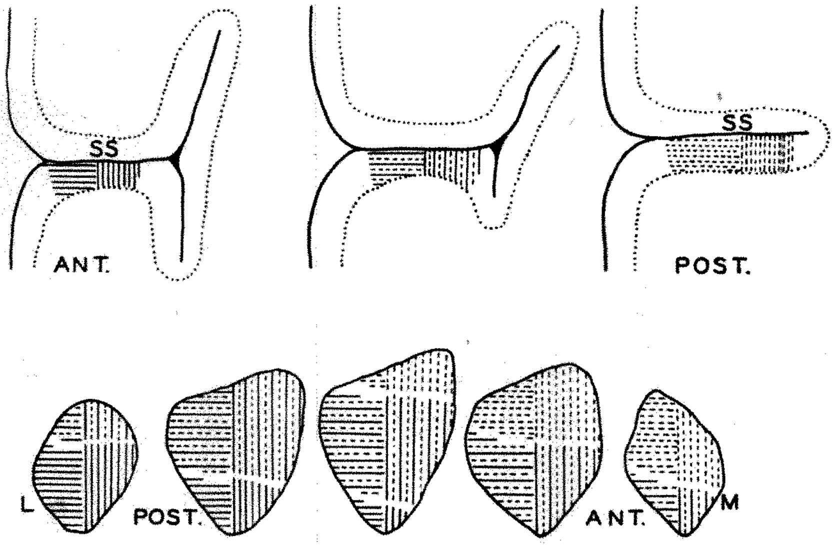

FIG. 16.—The geniculocortical projection in the macaque monkey after Walker. The projection of the medial geniculate body is to the similarly marked portion of the auditory koniocortex.

The present investigation lends support to a more restricted localization of the auditory projection area; the experiments are, however, still insufficient for a detailed analysis of its exact boundaries or spatial organization of the radiation. Certainly the fact that a small localized lesion of the superior surface of the temporal lobe produces an extensive zone of retrograde cell degeneration in the corresponding medial geniculate body, is strong evidence in favour of a focal auditory projection area. It is difficult to assess the degeneration of the medial geniculate body in the second experiment because part of the change is probably due to interruption of the auditory radiation and not to primary damage of the auditory "koniocortex." For this reason, it can only be concluded that the degenerated parts of the medial geniculate body projected to the posterior portion of the auditory "koniocortex" (fig. 16). The medial portion of the geniculate body sends its fibres to the inner or deeper parts of the cortex on the superior surface of the first temporal convolution. Walker concluded that roughly an anteroposterior plane projected upon each point of the cortex. By this means intricate integrations could be accomplished at the thalamic level. Whether such a schema will hold for the projection in the chimpanzee remains to be determined. Certainly the auditory projection appears to have precise topographical organization throughout its entire course.

IV.—SUMMARY.

(1) The normal structure and histology of the medial and lateral geniculate bodies of the chimpanzee are described in detail.

(2) The degenerations in the lateral geniculate body of two chimpanzees resulting from lesions of the striate cortex and visual radiation are described, and the projection of the lateral geniculate body upon the cerebral cortex is analysed.

(3) The degenerations in the medial geniculate body are described in two experiments following temporal lobe lesions. The observations indicate that the auditory projection area of the chimpanzee is probably sharply restricted as in the monkey, to a small area on the superior surface of the first temporal convolution, being largely hidden within the Sylvian fissure. The spatial organization of the projection is not yet determined.

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THE TONIC FOOT RESPONSE TO STIMULATION OF THE SOLE: ITS PHYSIOLOGICAL SIGNIFICANCE AND DIAGNOSTIC VALUE.

BY KURT GOLDSTEIN[1]
(*New York*).

THE following responses to stimulation of the sole of the foot are usually distinguished: (1) *the normal plantar flexion reflex* of the toes in response to a moving tactile stimulus, followed by a quick return of the toes to normal position ; (2) *the pathological, or Babinski plantar response.*

There remains another reflex phenomenon which has not hitherto received adequate consideration: namely, the slow tonic plantar flexion and adduction movement of the toes, with hollowing of the sole and some wrinkling of its skin.

This phenomenon, which we shall speak of as *the tonic foot response,* belongs to that group of tonic responses first described under the name of tonic innervation by Liepmann (1900), Goldstein (1909) and by Kleist (1932). Subsquently, examples of a tonic response to stimulation of the palm of the hand have been recorded under the title of " tonic innervation " by Wilson and Walshe (1915), "forced grasping" by Schuster (1923), Schuster and Pineas (1926), Adie and Critchley (1927) and by others. On the basis of their own observations Walshe and Robertson (1933) reached the conclusion that in the complex phenomena thus named two separable and distinct components are present: (a) " volitional grasping movements " in response to objects seen, or felt in the palm, and (b) " reflex tonic grasping " in response to stretch of the flexor muscles of the digits.

In a later publication Walshe and Hunt (1936) confirmed this view and concluded that the first (grasping movement) component is determined by mental factors, while the second (tonic grasp) is " exclusively a proprioceptive reflex reaction to stretch." Such a distinction had not been made by earlier observers though it is one of importance in understanding the nature of the phenomenon, with the result that the subject was involved in some obscurity.

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[1] (From the Columbia University and Montefiore Hospital, New York.) The author wishes to express his appreciation to the Rockefeller Foundation for special grants aiding him in this study, which was carried out under the auspices of the Harry H. Strauss Neurological Fund.

A general discussion of this problem is not now proposed here, but some new observations concerning the tonic component, especially the tonic foot response, will be recorded.

Schuster and Pineas were the first to observe it in the foot and called it "foot grasping." Later it was described by the present writer (1931), by Sittig (1932), by Freeman and Crosby (1929) and Russell Brain and Curran (1932).

Following the case reports there will be a theoretical discussion and a consideration of the diagnostic significance of the phenomenon.

CASE REPORTS.

Case 1.—A. R., a woman aged 21. She complained that for over two months she had developed a progressive weakness of the right side, sensory impairment in the right leg and severe left-sided headaches. On examination there was a right hemiparesis. The right hand showed defect of two-point discrimination and of appreciation of size and shape. There was also postural sensory impairment in the right arm. The tendon reflexes on the right were increased and the right plantar response was of the Babinski type. The right abdominal reflexes were absent. There was no tonic foot response.

There was exophthalmos of the right eye and bilateral papillœdema. A diagnosis of left parietal lobe tumour was made.

At operation a cyst was found in the sub-cortical region of the parietal lobe, 4 cm. from the mid-line on the left side. The cyst wall was dissected out and was later reported as glioblastoma multiforme. Two days after the operation, the patient complained of severe headaches and general weakness. The pulse rose from 88 to 120 and the temperature from 98° to 99·4° F. At that time, she had a clear-cut tonic plantar response on the left foot. No other pathological signs were seen on the left side. Right-sided symptoms were as before. After two days, during which the patient improved a great deal generally and the temperature and pulse returned to normal, the tonic foot response disappeared and was not subsequently observed during a period of some 11 months.

Since there was no evidence of a lesion of the right hemisphere we might at first glance assume that the tonic foot response is a homolateral phenomenon. However, a closer observation of the relationship between the onset and disappearance of the phenomenon and the general condition of the patient led us to consider the phenomenon as an expression of a functional derangement of the contralateral hemisphere. The phenomenon was only observed during the immediate post-operative period, that is, when the operated hemisphere was œdematous. We may assume that the œdematous hemisphere compressed the other hemisphere and thus disturbed it functionally. If this be so, we may relate the tonic response to this functional damage of the hemisphere contralateral to the limb where the phenomenon was observed. The fact that this tonic response was observed without any other abnormal sign on this side, notably without any pyramidal tract symptoms, leads us to regard it as an expression of but slight disturbance of cortical function. This case is not suitable for localizing the phenomenon in relation with any special region of the brain, but subsequent cases will show that the frontal lobe seems to be especially important in this respect.

Case 2.—J. G., a male, aged 42. Brain abscess.

Eight weeks' history of sinus infection followed by headache on the right side of the head, progressive weakness and sensory loss of the left face, arm and leg.

On examination there was a central type of weakness of the left side of the face, tongue and soft palate, flaccid left hemiplegia with increased tendon reflexes, transient ankle clonus and Babinski plantar response. All forms of sensation were impaired in the left side, and in the left hand postural sensibility and stereognosis were absent. A right frontal lobe abscess was diagnosed.

At operation the abscess was found in the posterior part of the middle frontal convolution. Three months later a second operation was performed to secure adequate drainage. The patient remained in bad general condition for some months, and after this period the physical signs were as follows: confusion, defective attention and memory for recent events, a strong sucking response to tapping of the *right* side of the mouth, a flaccid left hemiplegia with increased tendon reflexes, a variable Babinski plantar response. There was no forced grasping of the hand, but touching the *right* sole evoked plantar flexion of foot and toes which persisted for some time. The toes then slowly dorsiflexed and made quick alternating dorsal and plantar flexion movements. Of these dorsiflexion was the more rapid and became longer-lasting each time. Stimulation of the *left* plantar response also elicited this tonic response of the right foot.

Three weeks later the general condition was markedly worse. The tonic plantar response of the right foot was not so well-marked as previously. A bilateral Babinski response was obtained, and a grasping response of the right hand. The sucking response was present as before. A few days later the general condition became progressively worse, there was early papillœdema and the patient died with symptoms of meningitis.

Post-mortem examination.[1]—The right hemisphere was larger than the left and its convolutions were all flattened. The superior longitudinal sinus was shifted to the left, especially in the frontal region. There was a slight bulging of the right gyrus cinguli compressing the left hemisphere. The right lateral ventricle was constricted, the left slightly dilated. There was an irregularly shaped abscess in the region of the right insula. The temporal horn of the right ventricle was dilated, the third ventricle was obliterated and contained a little pus. There was pus within the horns of the right ventricle. The left hemisphere itself was not involved by the abscess.

In this patient with a right-sided brain abscess we found left-sided pyramidal tract symptoms and a tonic foot response on the right side.

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[1] The author is indebted to Dr. Charles Davison of the Neuro-Pathological Laboratories of the Montefiore Hospital for the gross and microscopic pathological reports, and the permission to use these reports.

The clinical facts may be interpreted as follows: as long as the abscess in the right frontal lobe did not press upon the left hemisphere the symptoms were confined to the left side of the body. Later, when the process in the right hemisphere increased and this hemisphere was swollen, the tonic foot response appeared as the first sign of pressure on the left hemisphere. With the increasing disturbance of the left hemisphere, a Babinski response also appeared on the right side, simultaneously with some decrease of the tonic foot response. At this point forced grasping and groping responses of the right hand and a sucking phenomenon of the right side of the mouth appeared. We are inclined to explain these phenomena in the following way. The tonic foot response is the first sign of functional derangement. With an increase of this the Babinski appears and may to some degree mask the tonic response. Later we shall see that both phenomena may be observed at the same time. The grasping of the hand may be considered as an expression of more severe disorder. The autopsy reports confirmed our assumption by the fact that the right hemisphere was greatly enlarged, and, by pressure displaced the left hemisphere. The relationship between the tonic response and the frontal lobe was also confirmed.

Case 3.—H. R., male, aged 30.

History.—Two and a half years previously the patient was noted to have a fit while asleep. There was stiffness of the extremities and shaking of the entire body for five minutes, then a deep unconscious sleep from which he could not be roused. These fits recurred at intervals of three to four months. The fits subsequently became more frequent and were later accompanied by headaches and vomiting. Vision was then noticed to be failing. The clinical diagnosis was tumour of the right frontal lobe.

Operation revealed an astrocytoma of the right frontal lobe. This was treated by X-ray therapy.

Neurological examination.—Six months later, the patient tended to fall asleep, was apathetic and unresponsive, disoriented, and showed a memory defect both retrograde and anterograde. Evidence of motor asphasia and of apraxia of the left extremities were observed. There was incontinence of urine. The left arm deviated and was coarsely tremulous, there was some weakness of the left side of the face and nystagmus on deviation to the left, with some weakness of right lateral deviation of the eyes. The left tendon reflexes were increased, the left upper abdominal reflexes absent, the lower feeble. The left plantar response was of the Babinski type. *Tonic plantar response to pressure on the right foot. Slight grasping in the right hand.* Bilateral sucking and biting responses to stimuli, right greater than left. The patient gradually got worse and died.

Post-mortem.—Right hemisphere larger than the left. The right frontal convolutions were flattened and apparently infiltrated by a neoplasm. The ventricles were filled with tumour tissue and were enormously dilated. The ependymal lining of the right ventricle was distorted and infiltrated by tumour tissue. Part of the tumour invaded the centrum ovale in the region of the inferior parietal convolutions. Cystic degeneration or porencephalic destruction was found in the white matter of the first and second frontal convolutions on the right. The corpus callosum was also partially infiltrated by the neoplasm. The tumour infiltration extended back into the anterior nucleus of the thalamus, the splenium of the corpus callosum and right hippocampus, septum pellucidum, fornix and left hippocampus. Hæmorrhagic areas were found throughout the thalamus, in the left dentate nucleus extending into the region of the left superior peduncles.

The lesion was in the right fronto-temporal region with pyramidal tract symptoms on the left side of the body. With an increase of the process there appeared a tonic plantar response on the right foot and a slight grasping of the right hand.

This case also reveals the connection of the tonic foot response with a functional disorder of the anterior part of the brain opposite the site of the lesion.

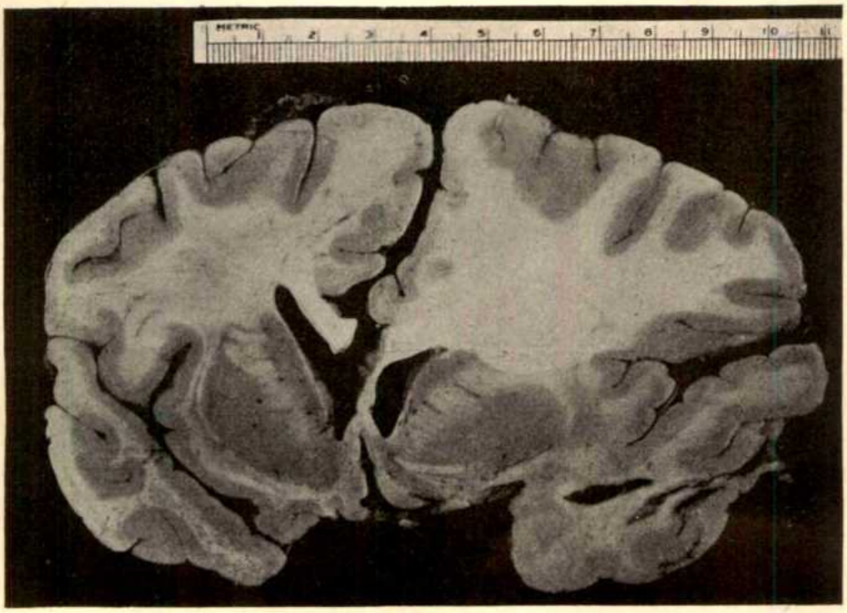

FIG. 1.

Case 4.—J. B., female, aged 40.

History.—She complained of " splitting " right-sided headaches for four or five months, ceasing spontaneously and reappearing one week after delivery of a child in the early part of May, 1935. She vomited and became confused and delirious on May 18, 1935, and continued in a state of mental confusion, somnolence and restlessness. Later she fell into a stupor.

On examination, she was acutely ill, showing bilateral papillœdema, bilateral 6th nerve weakness and left facial weakness. There was generalized hyper-reflexia.

The clinical diagnosis was tumour of the right fronto-parieto-temporal region. Operation on October 6, 1935. A deep sub-cortical glioma in right fronto-temporal region with a cyst was found. One year later, exposed to intensive X-ray therapy without improvement.

Neurological examination a year after operation revealed a left hemiparesis with increased tendon reflexes on both sides, especially on the left. There were bilateral Babinski plantar responses and bilateral tonic foot responses. Emotionally she was unstable, varying from euphoria to tears. She was restless, speech was indistinct and attention defective, though memory was fairly good. There was left homonymous temporal hemianopia.

Tonic foot responses were elicited bilaterally ; there was a sucking response on the left side of the mouth and grasping of the left hand. She went progressively downhill and died.

Post-mortem (Brain) (Fig. 1).—Flattening of practically all the convolutions of the right hemisphere. Right gyrus cinguli bulged slightly into the left gyrus cinguli. The brain stem and cerebellum as well as the right cerebral peduncle were pushed to the left. Marked œdema of the white matter of the right hemisphere with a constriction and slight dilatation of the right lateral ventricle. The right internal capsule was more prominent than the left. The thalamus and basal ganglia were compressed on the right. A tumour nodule was seen in the region of the temporal lobe and involving also the hippocampal and fusiform gyri. It was cystic in part of the inferior parietal convolutions.

This patient was especially interesting because she showed the Babinski and the tonic response at the same time. That these two phenomena are unrelated seems clear since they were elicited by different stimuli, a slight moving stimulus especially at the base of the toes evoking the Babinski response, while touch or pressure to the sole produced the tonic response. Further, this patient showed on stimulation of one side, the right, a tonic response on both sides.

From the post-mortem examination we are justified in assuming that the tonic response on the right side was due to the pressure on the left hemisphere, produced by the tumour in the right hemisphere. We may assume further that the tonic response was produced by the lesion of the frontal lobe, the Babinski by that of the motor area.

Case 5.—H. K., male, aged 55.

History.—Illness began in January, 1936, with frontal headaches, vertigo, blurred vision and subsequent left-sided hemiplegia.

Operation for a right frontal neoplasm, followed by deep X-ray therapy. Headaches disappeared and movements of the left arm and leg returned. In May, 1936, headaches and left hemiparesis returned with periods of unconsciousness. Some years previously he had been treated for lead poisoning, and had had tremors of both hands since that time.

Neurological examination.—Mental retardation, psychomotor restlessness and emotional instability. Slight bilateral papillœdema with secondary optic atrophy on the left. Left hemiplegia, left hemihypesthesia with astereognosis, fine tremor of the outstretched right upper extremity, uncertain and partial left homonymous field defect. Absent abdominal reflexes, tonic plantar response of the right foot, protrusion of lips to touch on right side of mouth. Course was progressively downhill and the patient died.

Post-mortem examination.—Right hemisphere slightly smaller than the left, dura adherent to the first and second frontal convolutions. Area of necrosis in white matter of right hemisphere, near the anterior tip of lateral ventricle. All frontal convolutions, except orbital, were obliterated. White matter markedly anæmic in frontal area of right hemisphere. Tips of frontal convolutions showed a necrotic zone and abscess-like area which communicated with the tip of the right lateral horn. Microscopic diagnosis: Astrocytoma.

Summary: Right frontal neoplasm, left sided symptoms were the first signs. Later there was a tonic plantar response of the right foot and a tonic response of the mouth musculature to tapping on the right side. Here the relationship between the functional disturbance of frontal lobe and the appearance of the tonic foot response on the side opposite the lesion is clear.

Case 6.—A. S., male, aged 30.

History.—For two years he had " difficulty " with his right eye and some twitching of the right side of the face, which at the end of this period spread to the hand and foot of the right side. At this time, also, there were severe right-sided headaches accompanied by dizziness and blurred vision. Later, he had a convulsion lasting for three hours and consisting of twitching of the right side, frothing at the mouth, tongue-biting and incontinence. There then developed memory defect, aphasia and an increase of convulsions to three daily. He was operated on twice, to relieve pressure and to remove a cyst, but the symptoms returned. Two further operations were followed by X-ray therapy. This led to a slight improvement, but was followed by a downhill progress.

Diagnosis was glioblastoma of the left fronto-parietal area.

On return to hospital, marked irritability and a tonic plantar response of the left foot. Grasping response in the left hand with an after-groping in the right hand. There was only a slight grasping response of the right hand. A tonic foot response was elicited to tapping on the right side, and there was a sucking response to lip stimulation. Two weeks later there was no tonic plantar response, only a slight grasping in the left hand with no after groping of the right hand, and no grasping in the right hand. The patient became much more cheerful and co-operative and showed marked improvement, and left the hospital.

In this case there appears the same relationship between a functional disturbance of the cerebral hemisphere by pressure and the tonic foot response on the side corresponding to the affected hemisphere. With a decrease of the primary process and improvement of the general condition and, as we may assume, a decrease of pressure on the opposite side, the tonic response disappeared.

This case showed other interesting phenomena. There was bilateral tonic grasping of the hands. With improvement in the patient's general condition this grasping diminished more on the side opposite the tumour than on the other side.

Case 7.—A. H., housewife, aged 52.

History.—For seven years she had been subject to "spells" in which she did not lose consciousness, but talked incoherently, was confused and convulsed on the left side. The twitching begins in the foot and spreads to involve the entire left side, including the face. The attack is preceded by a feeling of weakness of the left side, and is followed by transient weakness of that side. Sometimes the aura is not followed by an attack, and sometimes she is able to keep off an attack by squeezing the left hand with the right, for in the aura the fingers of the left hand spread wide apart. On the advice of her doctor she ceased work for sixteen months, during which time the attacks ceased, only to recur when she resumed work.

On admission to hospital the following signs were noted: The visual fields were normal. There was blurring of the nasal margin of the right optic disc and bilateral fullness of the retinal veins. She was normal mentally. There was a slight left hemiparesis, face, arm, leg, the leg being weaker than the arm. There was slight inco-ordination of the left hand and arm. The tendon-jerks were increased on the left, and there was a doubtful Babinski response on plantar stimulation of that side, but on stroking the skin below the external malleolus a more definite extensor plantar response was obtained. There was no sensory loss. A radiogram showed enlargement of the sella with thinning of the dorsum and posterior clinoid processes. A faint cloud-like shadow in the right frontal region suggested the possibility of calcification in a tumour. The encephalogram revealed displacement of the ventricular system to the left, with downward displacement of the right lateral ventricle, which was deformed posterior to the plane of the foramen of Monroe.

A provisional diagnosis of right frontal tumour was made. At operation no abnormal appearance was seen and no tumour found. Needle punctures gave a negative result. Two days following operation, the patient had two left-sided seizures followed by a flaccid hemiplegia. This slowly improved and tended to become spastic. She was discharged to the clinic one month after the operation.

Neurological examination (1937).—Since the operation, the symptoms are essentially as before, there is a left hemiplegia with spasticity of the extremities, and in the past two years the patient has been able to walk without a stick. Headaches have occurred, but not very severe, "like a band across" frontally and bilaterally. In the past few weeks, there has been some nausea but no vomiting. Hearing is diminished in the right ear (past six months). Intelligence shows marked change, similar to that commonly found in frontal lobe involvement, and attention is poorly sustained. Tendon hyper-reflexia is marked on the left, slight on the right. There is a Babinski response on the left and a tonic plantar foot response on the right. There is a tendency to slight tonic grasping in the left hand. Abdominal reflexes are diminished on the right, absent on the left. Retinal arteries are enlarged and veins engorged. The disc margins are blurred, but visible, and there is some atrophic pallor of the left disc.

In this case a suspected tumour of the right frontal lobe produced symptoms of a left hemiplegia. In addition, there was to be observed a tonic plantar foot response on the right side, as well as a faint grasping of the left hand. We may explain the tonic foot response as a sequel to the pressure of a right sided tumour on the left frontal lobe. The faint grasping in the left hand is assumed to be a symptom of the increasing infiltration of the neoplasm in the right frontal lobe.

II.—Discussion on The Origin of the Tonic Foot Response.

As Brain and Curran have described, the phenomenon is to be elicited by direct pressure upon the sole without a moving stimulus. I should like to add that in my experience an increase of the pressure, especially to the ball of the foot, leads to an increase of the response. Painful stimuli are similarly effective. The stimulus differs from that by which the Babinski response is elicited, the latter being produced by a stroking of the sole. It differs also from the stimulus by which the normal plantar response is elicited, which also consists of a light stroking.

The tonic phenomenon consists of a flexion and adduction movement of the toes, associated with a curving of the foot and wrinkling of the skin of the sole. It looks like an " Umklammerung," or clasping of the stimulating object (fig. 2).

Sometimes this is seen clearly when a pencil is placed at the base of the toes. The toes grasp the pencil. The movement is slow, the contraction persists with the stimulus, and also for a varying time after stimulation. It increases with continuation of the stimulus. Relaxation after removal of the stimulus takes place slowly in short jerks. The reaction has a very strongly forced character and in some cases cannot be inhibited by the subject. In individual cases there may be differences as to the duration and intensity of the reaction and as to the control of the individual over it.

This reaction has been found[1] to coincide with the finding of *damage of the frontal lobe* or of efferent fibres from this part of the brain. Lesions involving the medial aspect of the frontal lobe seem especially prone to produce it. Signs of a lesion of the pyramidal tracts (the motor area) may co-exist with the tonic response, but they are not related. This may be verified by the fact that they are to be elicited by different stimuli. Sometimes severe pyramidal tract lesions seem to cover or mask the tonic response. The tonic response is a sign of slight damage of the frontal lobe, of which it seems to be the first expression. Therefore, it is to be observed not seldom on the side homolateral to an expanding lesion of the brain,

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[1] Observation of a large number of patients during *insulin treatment* showed that a markedly developed tonic foot response is a very common finding in this condition. The phenomenon appears relatively early and remains for a very long time. If the Babinski is present, sometimes the former phenomenon disappears, or, at times, both reactions can be elicited. The tonic foot response is frequently accompanied by a grasping in the hands and by a tonic phenomenon of the lips.

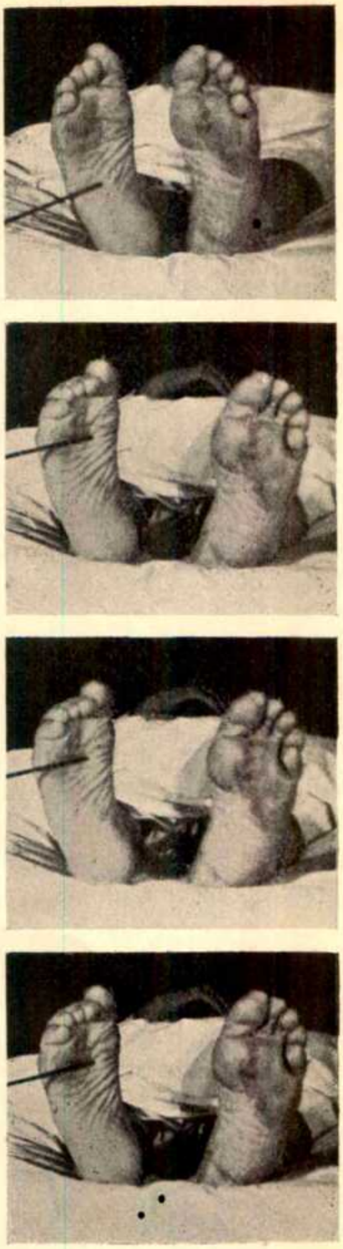

FIG. 2.

namely, when there is involvement of the opposite side by pressure. The tonic foot response is essentially a contralateral symptom, but its homolateral appearance is particularly characteristic of brain tumours. If the causative involvement of the frontal lobe increases, especially if it should involve the more lateral regions of this lobe there also appears a tonic response in the hand, and a tonic response in the lips of the same side.

III.—The Nature of the Tonic Foot Response.

There is no doubt that the tonic foot response is of a similar character to the tonic grasping of the hand. Our conception of the nature of the tonic foot response is therefore determined by our conception of the tonic grasping of the hand. The latter has usually been considered as a release of a phylogenetic reflex or as a compulsive normal grasping, or as a grasping reflex of infants, inhibited in adults. That this phenomenon is not caused by the reappearance of a subhuman reflex is to be seen in the fact that tonic foot-grasping, according to the investigation of Brain and Curran, is not observed either in (adult) monkeys or in anthropoid apes.

As I have explained elsewhere (1931), the so-called forced grasping of the hand has nothing to do with the normal grasping of adults, but is a pathological phenomenon, an expression of an abnormal reaction to stimuli, corresponding to reactions characteristic for parts of the nervous system isolated from the higher centres. As I have suggested (1936), every reaction of the organism starts with a turning-to movement of the organism towards the stimulus object, by which the organism achieves a connection with this object. Normally, this first step is followed by the reaction corresponding to the task which the situation demands and therefore represents only a short transient part of the reaction. Under some pathological conditions this " turning-to " movement appears isolated and gains by this isolation an abnormally forced appearance. This is to be observed especially in lesions of the cerebellum and frontal lobe. One expression of this abnormal " turning-to " reaction is the so-called forced grasping of the hand. I believe the same is the case in the tonic plantar response of the foot. With this consideration it is intelligible that a very simple stimulus such as pressure or touch is sufficient to elicit the reaction, and, further, that an increase of the stimulus leads to an increase of the reaction. The fact that this tonic response is also elicited by disagreeable stimulation makes it appear very unlikely that forced grasping has anything to do with normal grasping. The normal individual is not inclined to grasp disagreeable objects. Therefore the phenomenon should not be called forced grasping but rather an *abnormally forced " turning-to " movement.*

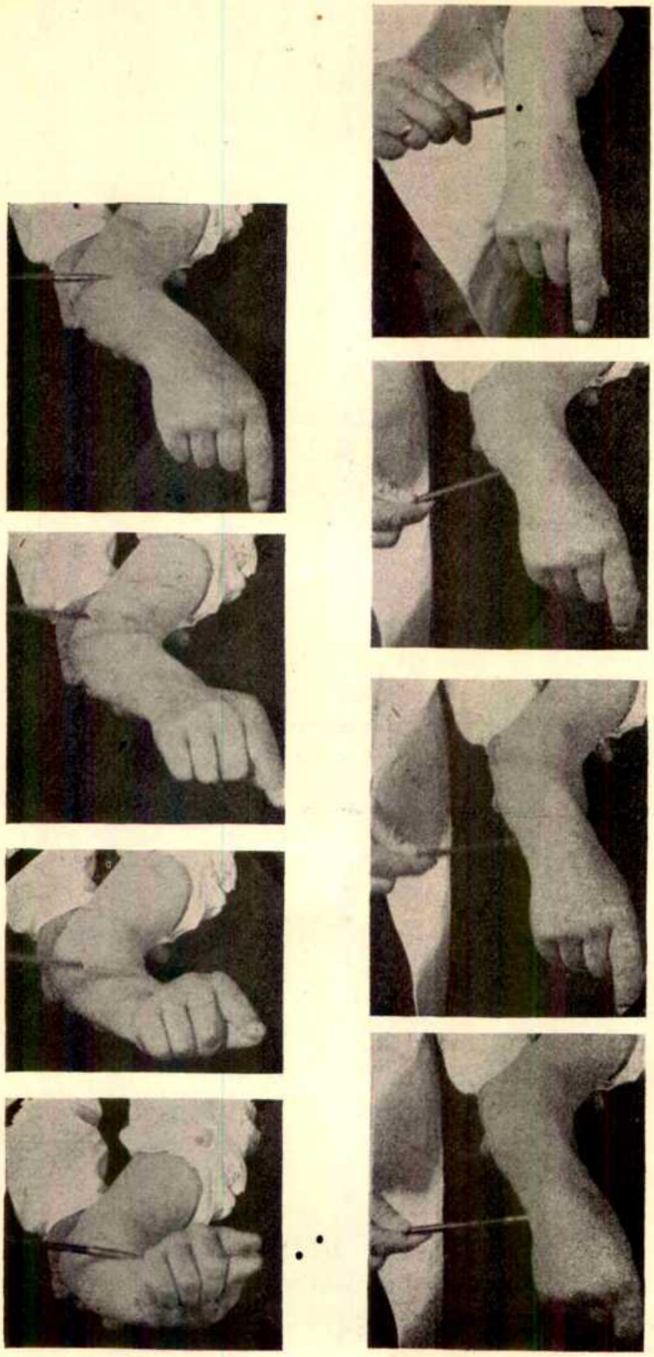

FIG. 3.

That the phenomenon under discussion has nothing to do with the grasping of an object, but represents a forced turning toward the stimulus, is to be seen in an observation which may be made in some patients with so-called forced grasping of the hand. If, instead of the palm, the dorsal side of the hand be stimulated, then we may observe a movement of the same forced character, directed not palmarward but dorsally (fig. 3). Such a reaction cannot have anything to do with grasping but is intelligible on the same principle as the so-called grasping, namely, as an expression of an abnormal " turning-to " movement towards the stimulus. One particularly clear example of the dorsal reaction has been published in my former clinic by H. Cohn (1930).

I have seen a corresponding phenomenon in the foot in a case of tonic foot response. On stimulating the dorsiflexors of the toes, after a certain time there appeared a slow dorsal movement of the toes, especially of the big toe, increasing with the continuation of the stimulus and persisting for some time after its cessation.

The so-called forced grasping also has nothing to do with the very intense grasping of children. However, in early childhood, we may observe a forced clasping of the hand which disappears gradually as the child learns to use his hand, i.e. becomes capable of real grasping. This forced clasping corresponds to the pathological grasping, so-called forced grasping of the adults. It is an abnormal " turning-to " movement. It corresponds to the isolation of the function of the concerned brain centres, as a result of the immaturity of the higher centres in early childhood. For the same reason we observe a tonic foot response in children and its disappearance later than the phenomenon in the hand is intelligible because the child only learns later to use his foot for a purposeful movement. Brain and Curran have observed that the tonic response does not usually disappear before the ninth month of life, sometimes much later. My observations lead me to agree with these authors and with the similar description of the phenomenon which Sittig has given. The latter's observations accord with those of Brain and Curran as to the presence of the tonic foot response in young monkeys—but not in adults. This view of the tonic foot response makes it easy for us to understand that patients who present the tonic foot or hand phenomenon also present a similar type of phenomenon of the lip: this has usually been called a sucking reflex. I shall not discuss here whether there is such a thing as a true reflex in adults corresponding to the sucking of an infant. The phenomenon under consideration is not related to sucking. This becomes clear since we are able to observe the phenomenon on one side only. A tap on the lip is followed by a unilateral pouting movement and closing of the lips, a pattern which does not correspond to sucking. It corresponds to the other forms of tonic response to stimulation, in the sense of a " turning-to " movement, and is only another expression of this.

IV.—The Diagnostic Significance of the Tonic Foot Response.

As we have seen, these tonic responses appear as the first signs of an involvement of the anterior part of the cortex, especially of the frontal lobe, even earlier, as I believe, than the Babinski sign or other pyramidal tract signs. Therefore they possess a diagnostic value for a lesion in this region. The tonic response of the foot arises especially with a lesion of the medial part of the frontal lobe, and a lesion which involves the lateral parts of this region is also followed by tonic hand grasping and a tonic lip response. Should these phenomena be combined with pyramidal tract signs, we may then assume an associated lesion of the motor area. The tonic foot response is of special interest in cases of brain tumour since its appearance on the side homolateral to the tumour allows us to assume that the disease process has taken on a progressive character and presses upon the crossed hemisphere. Thus it may well be the first sign of œdema of the brain after operation for a tumour.

Summary.

(1) This study is concerned with the tonic response of the foot to stimulation of the sole. The character of the reaction is described. It is a slow movement, elicited by touch or pressure to the sole of the ball of the foot. Increasing stimulation, especially if painful, leads to an increase of the movement. The posture persists for some time after cessation of stimulation and then the foot slowly returns to its habitual position.

(2) A relationship is suggested between the tonic foot response and lesions of the frontal lobe. This tonic response is considered as one of the earliest signs of a lesion of the frontal lobe. It appears earlier than the Babinski response or other pyramidal tract signs.

(3) Therefore the tonic foot response has a special diagnostic value, especially when it appears on the side homolateral to a lesion of the frontal lobe. It then indicates that the affection of the one frontal lobe is pressing upon the frontal lobe of the other side or that there has been a spread of the process into the crossed side. It is a symptom which points especially to a lesion of the medial part of the frontal lobe.

(4) The tonic foot response, in the same way as the so-called forced grasping of the hand, is not related to the normal phenomenon of grasping. It is an expression of an abnormal " turning-to " movement of the organism to the stimulus object, and appears as a response of the lower mechanisms when the " higher centres," especially of the frontal lobes, are damaged.

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NOTE ON THE NUCLEUS RUBER MAGNOCELLULARIS AND ITS EFFERENT PATHWAY IN MAN.[1]

BY KARL STERN.

INTRODUCTION. SURVEY OF PREVIOUS LITERATURE.

THE large-celled red nucleus (n. ruber magnocellularis) has a direct uninterrupted connection with the lower motor neuron through the rubrospinal tract (v. Monakow, 1909-1910). The experimental work on the red nucleus (Rademaker, 1926) has been done on those animals in which the large-celled part is the main part and the rubrospinal tract is a prominent bundle. The results of this experimental work can only be applied to

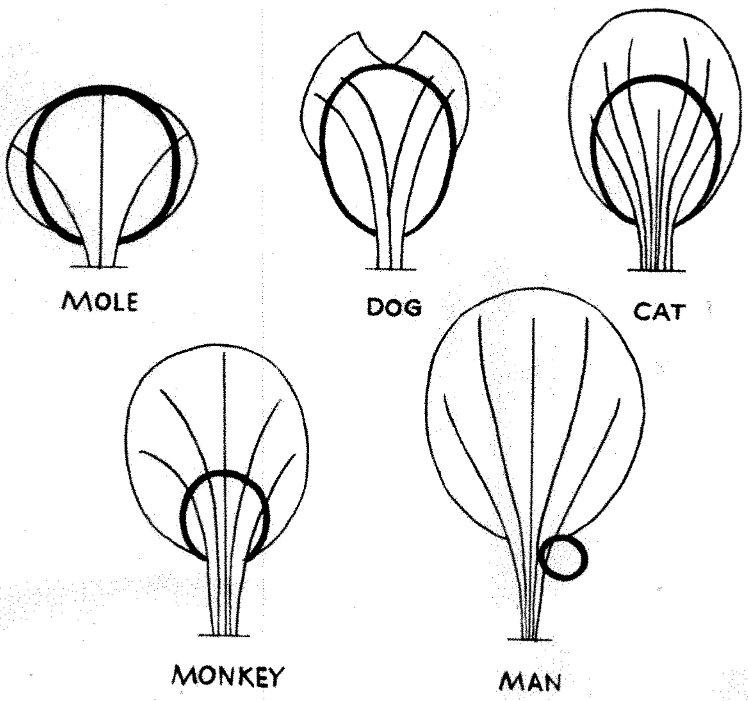

FIG. 1.—Proportion and topographic relation of the large-celled (thick line) and small-celled (thin line) red nucleus in various mammals and in man. The fibres indicate the superior cerebellar peduncle, the horizontal line the level of its decussation. (Schematic drawing, modified after Winkler.)

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[1] From the Pathological Laboratory of the National Hospital, Queen Square, London.

human physiology if a homologue of the nucleus ruber magnocellularis and a rubrospinal tract exist in man. This, however, has been doubted by recent investigators. The present contribution is an attempt to throw more light on this question.

It is well known that in man the red nucleus is in its cyto-architecture and in its fibre-tract connections a complicated centre and very different even from that of the anthropoid apes (fig. 1). von Monakow (1910) concluded from certain morphological features that a small residuum of the n. ruber magnocellularis existed in man. Its position is the level of the "nucleus albus" of Stilling (the brachium conjunctivum oral to its decussation), the caudal tip of the main red nucleus and the transition between the nuclei of the 3rd and 4th nerves. Small clusters of giant cells of a "motor" type may be found in two different places in the cross section (fig. 2). One group is ventral and lateral to the 3rd nucleus, between the latter and the centre of the brachium conjunctivum, the other group is dorsal to the substantia nigra, between the latter and the brachium conjunctivum. This distribution, however, and the size of the

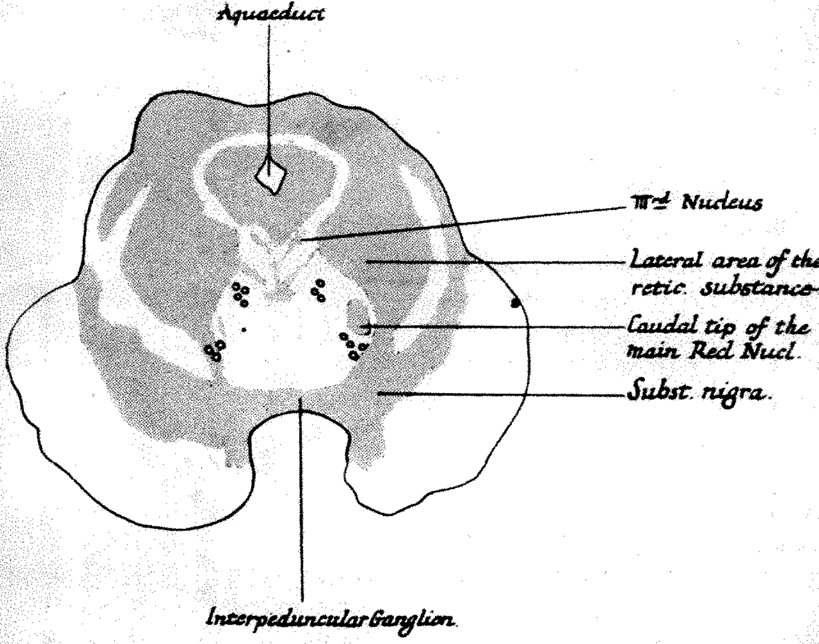
Aquaeduct
IIIrd Nucleus
Lateral area of the retic. substance
Caudal tip of the main Red Nucl.
Subst. nigra.
Interpeduncular Ganglion.

FIG. 2.—The grey formations of the human mid-brain at the level of the caudal tip of the red nucleus. The small circles indicate the position where the few giant motor cells can be found which are regarded as a residuum of the n. ruber magnocellularis. (Half-schematic.)

groups vary greatly with different individuals. In a caudo-oral direction they occupy only a short distance and on the average one finds not more than about three cells in one section (Winkler, 1929). In spite of the presence of many elements of the reticular substance and of unpigmented cells of the substantia nigra the cells are easily recognizable. The characteristic way in which they are suspended within the network of the fibres of the 3rd nerve and of the superior peduncle, and their size and Nissl structure made Monakow regard them as the homologue of the large-celled red nucleus.

This morphological identification, however, is not wholly sufficient, because cells of exactly the same appearance are to be found in the reticular substance of the medulla oblongata in man (n. motorius gigantocellularis, Jacobsohn, 1909). Therefore it has also to be proved that a rubrospinal tract arises from the mesencephalic group of cells. It can easily be realized that a fibre tract originating from these cells must be very fine, and its degeneration difficult to detect.

The evidence that this tract exists in man is very scanty. In the comparatively large literature on mesencephalic lesions with resulting degenerations of efferent systems (Collier and Buzzard, 1901, Raymond and Cestan, 1902, Haenel, 1902, Halban and Infeld, 1902, Marie and Guillain, 1903, Gordon Holmes, 1904, H. Claude, 1912, Souques, Crouzon and Bertrand, 1930, André-Thomas, 1936) only two reports of degeneration of the rubrospinal tract (Collier and Buzzard, and Gordon Holmes) are to be found.

Among the cases of thrombosis of the posterior inferior cerebellar artery described in the literature there is none which shows a secondary degeneration of the rubrospinal tract in the spinal cord (André-Thomas, 1936) although its situation in the retro-olivary area would lead us to expect this. Déjérine and Long (1912) in their study of a complete transverse lesion of the cervical cord in man did not see any degeneration of the rubrospinal tract caudal to the lesion.

The opposite method, i.e. to look for retrograde degeneration of the n. ruber magnocellularis, following medullary or spinal lesions appears more promising. It has, however, been used in very few cases (Monakow, 1910, Winkler, 1929). Monakow described a case of cervical syringomyelia in which the cells of the n. ruber magnocellularis had disappeared. Winkler, however, remarks that in such long-standing cases a transneuronal degeneration resulting from lesions of afferent pathways cannot be excluded with certainty.

Gagel (1932) in examining Foerster's cases of chordotomy reported that

PLATE XV.

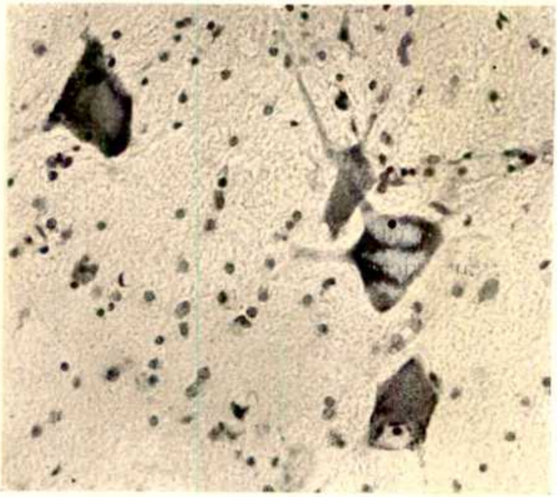

FIG. 3.

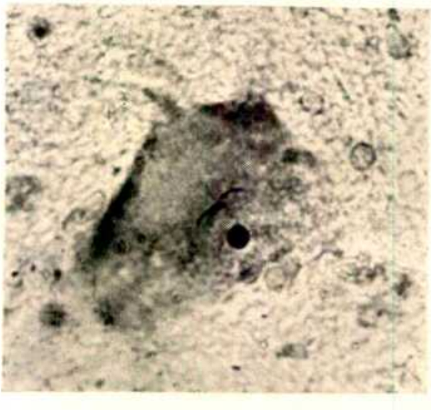

FIG 4*a*.

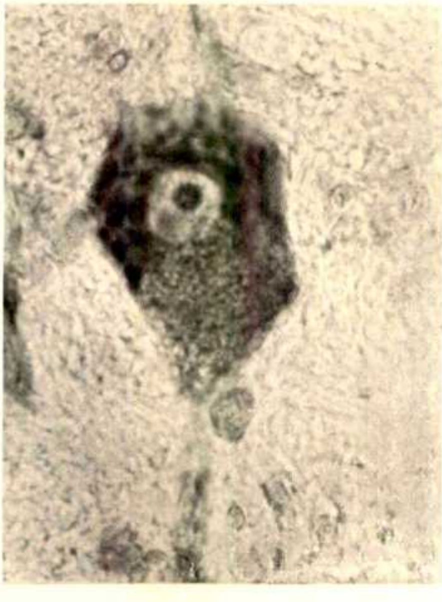

FIG. 4*b*.

FIG. 3. *Case 1.*—Cells of the n. ruber magnocellularis. Typical retrograde cell change. (Nissl. × 200.)

FIG. 4*a*. *Case* 2.—Cell in the n. ruber magnocellularis on the left side. Retrograde degeneration. (Nissl. × 750.)

FIG. 4*b*. *Case* 2.—Normal cell of the n. ruber magnocellularis on the right side. (Nissl. × 750.)

To illustrate Article by Karl Stern

he did not see any retrograde changes of neurons in the medulla oblongata or mid-brain except in Deiters' nucleus.

André-Thomas (1936) reporting one case of a mesencephalic lesion and reviewing the literature on the same type of case doubts the existence of a rubrospinal tract in man and criticizes the few positive findings.

Personal Observations.

For this investigation two cases were chosen in which (considering the interval between lesion and death) one would expect signs of retrograde degeneration in the cells of the large-celled red nucleus provided there was an uninterrupted pathway.

(1) *The first case* (F. C., P.M. No. 32, 1936) is one of paraplegia from invasion of the spine by a bronchial carcinoma. The patient, a man aged 40, had suffered for six weeks from a feeling of deadness from the chest downwards and from inability to move the legs. These symptoms had developed within three days. He had lost control of his sphincters.

On examination there was complete sensory loss and complete paralysis below the 4th thoracic segmental level. He developed bronchopneumonia and died six weeks after the onset of his neurological symptoms.

Post-mortem examination (Dr. J. G. Greenfield) revealed a bronchial carcinoma with extrathecal spinal metastases. There were carcinomatous masses in the muscles of the right side of the spine between the first and second ribs. The laminæ were soft at these levels. Inside the canal there was a mass at the level of the 2nd thoracic body and opposite the 6th thoracic body. The cord was completely softened from the lower end of the 4th to the 10th thoracic segments. There were a few secondary growths of the size of a split pea in the frontal lobe. The rest of the cerebrum, the cerebellum and the brain-stem were free from secondary growths.

Microscopical examination of the cord in the softened area showed that the softening occupied practically the entire cross section and was most marked centrally.

The microscopical examination of the mid-brain in the area of the large-celled red nucleus by serial sections 15 μ thick and stained by Nissl's method showed a perfect Nissl structure in the cells immediately adjoining the nucleus ruber magnocellularis (e.g. nucleus of the 3rd nerve, substantia nigra, mesencephalic nucleus of the 5th nerve). The glia was normal everywhere. The large-celled red nucleus was represented chiefly in the dorsal area, where cells in every section showed the typical picture of a retrograde chromatolytic change. On the right side the abnormal cells could be seen in clusters (fig. 3), on the left side as single cells and groups of two or three distributed over several sections.

(2) *The second case* (H. B., 1936) was one of thrombosis of the posterior inferior cerebellar artery. A man of 48 suddenly became ill with the typical symptoms of the lateral bulbar syndrome. There was partial loss of use, and gross ataxia and asynergia of his right arm and leg, a complete anæsthesia of the right half of the face, hoarse voice, and a loss of sensation to pain over the left half of the body and

the left limbs. He died fourteen days after the onset of the illness. Post-mortem examination showed an infarction of the right posterior inferior cerebellar artery. The typical triangular retro-olivary area in the medulla oblongata was necrotic with a complete loss of myelin sheaths.

The mid-brain was examined in serial sections (15 μ thick) every fifth and sixth of which were stained. The available blocks extended from the middle of the anterior colliculus down to the " nucleus albus."

Many nerve cells showed a marked degree of lipoid change. Nevertheless the Nissl structure in the cells of the 3rd and 4th nerve nuclei and of the substantia nigra was clear. In a section of the large-celled red nucleus, which in this case lay chiefly in the ventral position, retrograde chromatolytic changes were seen in all the cells on the left side (fig. 4*a*). The cells on the right side were normal (fig. 4*b*). The same difference could be seen in adjoining sections. By staining only the fifth and sixth sections a part of the large-celled red nucleus was unfortunately lost.

The appearance of the main red nucleus was normal. So was the appearance of the field of the reticular substance lateral to the nucleus albus (area parabigemina of Mingazzini) which Winkler regards as another residuum of the " palaeo-rubrum." The nerve cells in this area, however, show normally an irregular Nissl pattern and eccentric nuclei so that retrograde changes cannot be stated with certainty.

From the two cases described we may conclude that the few large motor cells at the caudal end of the red nucleus possess axons which reach at least as far as the upper thoracic cord, that these axons cross above the level of the medulla oblongata and that they pass through the retro-olivary area. This study affords further evidence that a residuum of the " palaeo-rubrum " and a true rubrospinal tract exist in man. On the other hand it demonstrates the extremely small size of this system in man compared with that of the animals commonly used for experiments, and shows how careful we must be in applying the results thereby obtained to the physiology of the human red nucleus.

SUMMARY.

In a case of spinal transverse lesion at a high thoracic level and in a case of thrombosis of the posterior inferior cerebellar artery the n. ruber magnocellularis (v. Monakow) was investigated for retrograde chromatolytic changes. In the first case such changes were present on both sides, in the second case they were confined to the side opposite to that of the lesion. These findings may be regarded as evidence that a rudimentary " palaeo-rubrum " and rubrospinal tract exist in man, a question which is still the subject of discussion in the literature.

I wish to express my gratitude to Dr. J. G. Greenfield for the use of his material and his post-mortem records, and for the suggestions which he gave me during this investigation.

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THE LOCAL SWEAT RESPONSE TO FARADIC STIMULATION.[1]

BY R. W. WILKINS (BALTIMORE), H. W. NEWMAN (SAN FRANCISCO), J. DOUPE (WINNIPEG).

(From the Research Unit, National Hospital, Queen Square, London.)

It has been found that stimulation of the skin by alternating or faradic current causes secretion of sweat in the surrounding area. In the present paper this response is described together with some experiments carried out to determine its mechanism.

METHODS.

The stimulating current was applied by a needle electrode which was guarded to within 1 mm. of its tip. This permitted adequate contact with a minimum of trauma to the skin. The indifferent electrode, a zinc pad moistened with saline, was strapped to the skin some distance from the area under observation. The current was derived from an audiometer circuit which allowed the regulation of frequency, amperage and voltage. Unless otherwise stated, the stimulating current was 0·25 to 0·5 milliampere at 50 cycles per second for one minute. Sweating was detected by the method of Minor (1929). After the selected area of skin had been cleansed with ether it was painted with a solution consisting of iodine 1·5 grm., oleum ricini 10 c.c. and absolute alcohol 90 c.c. When this had dried the area was lightly dusted with powdered starch. Sweat was easily recognized by the appearance of blue-black dots on the light-brown background. The majority of observations were made on the fore-arm of subjects in a moderately warm state. The subjects consisted of a group of five normal young adults and a group of ten patients with lesions of the nervous system. The site of the lesions will be described with the results obtained in these subjects.

RESULTS.

General description.—Approximately 200 observations have been made on the volar surface of the forearm. The usual response consisted of sweating around the point of stimulation in an oval area approximately 3 by 5 cm. disposed longitudinally in the axis of the limb. The response

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[1] Work done while Dr. Doupe held a Halley-Stewart Research Fellowship, Dr. Newman a Rockefeller Fellowship, and Dr. Wilkins a Fellowship of the American College of Physicians.

commonly extended slightly further in the distal direction, and its borders were irregular. Not infrequently a group of glands 8 or 10 cm. from the point of stimulation and generally situated distally were activated. There was, however, considerable variation in the area of the response obtained from stimulation of different points.

The sequence of events was as follows. After a latent period of ten to fifteen seconds from the beginning of stimulation, secretion, as shown by the appearance of discrete blue spots, began in the glands closest to the point of stimulation, and then spread to glands in the more outlying area. At the same time that those farthest away showed evidence of secretion some of the more central glands were still inactive. The intensity of the response in terms of the number of glands was greatest near the site of stimulation and not infrequently the blue spots coalesced. Sometimes the border was fairly sharp, while at other times it was vague, with the secreting glands separated widely at the periphery. The amount of sweat secreted by individual glands also appeared to be greater nearer the point of stimulation. In several instances after the cessation of the stimulus fresh spots appeared. When the duration of stimulation was prolonged to five minutes, few fresh spots appeared after the first minute, but the amount of sweat secreted increased with the duration of the stimulus.

The pilomotor response described by Lewis and Marvin (1927) appeared some two to five seconds before sweating was evident. While the areas involved were approximately the same size, the distribution of the goose flesh and secreting glands did not always coincide.

General conditions necessary for the production of the response.—The response was most easily elicited in subjects who were on the verge of sweating and when the skin was warm. It was, however, obtained even when the subject was so cold that he was shivering. In this instance the response was augmented in size and intensity by shining a warm light on the part under observation. This indicated the importance of the temperature of the skin, which was shown in another way. Two flat-bottomed test tubes 1 cm. in diameter were applied to the skin 1 cm. apart. One was filled with ice water and the other with water at 45° C. Stimulation at a point midway between the two tubes produced a response which was deficient under the cold tube and intensified under the hot.

Variation in different regions of the body.—The response on the forearm has been described above. Very rarely were points encountered which on stimulation gave rise to no sweating. Changing the position of the electrode by as little as 2 to 3 mm. was sufficient to enable a good response to be obtained. Observations on other parts of the body showed that the degree of response was roughly parallel to the number of sweat glands present in the regions examined, as given by Kuno (1934 *a*). On the forehead near the mid-line the response was intense and fairly linear in a vertical direction. It did not cross the mid-line in three normal subjects and in three subjects with unilateral root section of the 5th sensory root. In the latter the sweat response did not spread from the anæsthetic area across to the normal side, nor in the reverse direction. More laterally on the forehead the response was sparse, as it was also on the anterior surface of the chest, the thigh and the calf. On the dorsum of the foot a moderate response was obtained, which was again disposed in the long axis of the member. On the chest an attempt was made to determine if the response crossed the mid-line. Stimulation at a point 1 cm. to the right of the mid-line produced sweating which extended 1 cm. to the other side. Owing to the small size of the response in this region it was not possible to obtain evidence sufficient to exclude the possibility of this spread to the other side being due to overlap across the mid-line.

It has been noticed that sweat appeared on the palms regardless of the site of the stimulus. This was interpreted as a response to the pain. When the stimulus was applied to a point on the palm the usual local response was not obtained; on the contrary the diffuse palmar sweating arising from the pain of the stimulus seemed to be locally inhibited.

The stimulus.—Various types of stimuli were used in an attempt to provoke the local sweat response. Injury to the skin by crushing and other forms of trauma caused no sweating, even though a well-marked flare developed. Intense heating by focusing the rays of a powerful lamp on a spot 2 to 3 mm. in diameter caused a slight production of moisture in the area heated, but no suggestion of a spreading response. Kuno (1934 *b*) in a similar experiment failed to obtain any evidence of a spreading response beyond the area locally heated. Stimulation with a constant direct current of 1 milliampere or with an alternating current of 25 milliamperes at frequencies above 10,000 cycles did not produce sweat. The optimum frequency for the production of the response was investigated by choosing a point on the fore-arm which on stimulation at 50 cycles gave a good response. To this point repeated stimulations at varying frequencies for one minute were applied and the results compared. The optimum frequency was found to lie between 10 and 30 cycles and the limits between 5 and 10,000 cycles.

Latent period.—The latent period before the appearance of sweat varied with the strength and frequency of the current. Using 0·25 milliampere at 50 cycles it ranged from ten to twenty seconds. That the stimulation had produced some effect before this time was indicated by the following observation. In response to a current of 0·1 milliampere at 50 cycles sweat appeared at twenty-six seconds. The area was then reprepared and the same spot stimulated with the same current for periods of three seconds at one-minute intervals. Sweat appeared during the third period of stimulation. It was thus apparent that some change had occurred in the glands within three seconds of stimulation and that this state continued after the cessation of the stimulation. It was also found that prompt re-stimulation of a spot from which a good response had been obtained occasionally produced immediate sweating. It was not possible to demonstrate what portion of the apparent latent period was required for mere filling of the ducts of the glands.

Constancy of the response.—Maximal stimulation at one spot on repeated occasions produced responses of the same general configuration with the same glands participating. This was found by careful experimentation with a magnifying lens, the spots being related to lines drawn on the skin with Ziehl-Neelsen stain. Local heating of part of the area involved in the response during the stimulation increased the amount of sweat secreted but not the number of glands secreting in the part heated.

Area of overlap.—It was readily demonstrated by a series of stimulations at a number of points separated by 0·5 cm. that the areas of the different responses showed considerable overlapping. The borders of the response did not shift regularly with the change in site of the stimulus, but due to the wide variations in the size and shape of the response produced from different points no further conclusion could be drawn from this procedure. A more particular examination of the response of one gland was made with a magnifying glass. This showed that the same gland could be activated by stimuli applied at points 2 cm. apart, although very many of the glands which partook in the one response did not do so in the other, and the general configuration of the two responses was dissimilar.

Nervous pathways.—That the response was dependent on nervous connections was repeatedly shown in normal subjects by the absence of the response after laying down a novocain wheal at the site of the stimulus. A control injection of normal saline did not alter the response. Further evidence was obtained in a patient who had sustained trauma to the right brachial plexus seven months previously. There was complete wasting of the fore-arm muscles and complete loss of sensation in the segmental distribution C5 to D1. Stimulation in the anæsthetic area gave no response even though the part was artificially warmed. The possibility that the sweat glands in this region had become atrophied was excluded by the widespread sweating induced by the intracutaneous injection of 0·1 c.c. of 5 per cent. mecholyl. Stimulation of the normal arm in this subject produced a marked response. An intact peripheral nervous system is thus a requisite for the production of the response. In two individuals who had undergone excision of the stellate ganglion some years previously no response was obtained in the arm deprived of its post-ganglionic sympathetic nerve fibres. It appeared, therefore, that an intact post-ganglionic sympathetic innervation was necessary. Two patients with section of the thoracic sympathetic trunk immediately below the stellate ganglion and two with lumbar sympathectomy had normal responses in the affected areas. That the operative procedures had been successful and that regeneration had not occurred in these cases was shown by the complete absence of sweating on the palms or soles in response to a painful stimulus. This simple test offered a very precise criterion for the determination of the continuity of the pre- and post-ganglionic sympathetic nerves. The results obtained in these subjects showed that the pre-ganglionic connections of the sympathetic fibres were unnecessary for the production of the local sweat response to faradic stimulation. It was then shown that the ganglion itself played no part by three experiments in which a cutaneous nerve was blocked with 2 per cent. novocain. It has been repeatedly shown that this procedure prevents sweating of central origin in the peripheral area of anæsthesia, yet in this area the local response was obtained with ease.

Attention was next given to the mode of spread of the response. The fact that repeated stimulations of one spot always activated the identical group of glands suggested that a nervous connection existed between the point of stimulation and the glands. This was confirmed in the following way. First, it was determined that an intradermal injection of normal saline in no way affected the response. Secondly, on fifteen occasions 0·1 c.c. of 2 per cent. novocain was injected intracutaneously to form a small wheal. Stimulation on top of the wheal caused no response. Stimulation slightly to either side of the wheal produced sweating in the usual area, except on the surface of the wheal and in a segment on the opposite side. The borders of the small region where sweating was absent were not strictly radial, but appeared to be more nearly parallel and separated by approximately the width of the wheal. This was true so long as the wheal had a diameter greater than 0·5 cm. A smaller wheal permitted the passage of the response around it. That even such small wheals were effective in blocking the nerves was indicated by the observation that stimulation in the zone of anæsthesia around and on top of the wheal produced no response. Furthermore, it was found that the effect of a sweat-stimulating drug, mecholyl, which introduced intradermally rapidly diffuses and gives a wide area of sweat (Myerson *et al.*, 1937) was not altered by intradermal novocain, except that sweat did not appear on the wheal.

Using the rubber band technique of Lewis (1937) it was found that the nerves mediating the responses were relatively undisturbed by pressure. On three occasions a tense rubber band 10 mm. in width was placed across the volar surface of the fore-arm. It was found that stimulation to either side of the band caused sweat to appear on the other side. This phenomenon was still present after 30, 37 and 120 minutes, at which time there was well-marked analgesia in a tongue-shaped area extending 3 to 4 cm. distal to the band.

Incidental observations.—Stimulation to one side of an intradermal injection of 0·2 c.c. of 0·2 per cent. atropine inhibited sweating locally, but did not otherwise affect the spread of the response. A wheal produced by an injection of 0·05 per cent. prostigmin showed an augmented response on its surface after stimulation to one side of it.

Discussion.

It is recognized that electrical stimulation is an unnatural means of producing sweat and that this response may not occur physiologically in a normal subject. However, the activity of a sweat gland induced by this means has apparently the same peripheral mechanism as that brought about by normal innervation, for it is inhibited by atropine, augmented by prostigmin, and has the same relationship to the temperature of the skin (Kuno, 1934 *c*). That sweat glands themselves and not simply their smooth muscle fibres are stimulated by the faradic current is indicated by the observation that continued and increasing quantities of sweat could be produced by prolonged stimulation. The possibility that spread of current may directly stimulate the glands is ruled out by the observations that stimulation at certain points is ineffective, while a slight shift in the position of the electrode produces a good response, and that stimulation over very small wheals of novocain does not produce the response.

It has been shown that this local sweat response to faradic stimulation is dependent on the integrity of sympathetic fibres to the skin, but that it is independent of their ganglionic connections. It is possible that following stimulation locally a substance is produced which diffuses radially from the point of stimulation. It is apparent, however, that the diffusion of a sweat-producing substance would not explain the constancy of the response nor the blocking action of intradermal novocain on the spread of the response. The length of the latent period does not require a process of diffusion; this is especially so as it has been shown that a stimulus has some effect on the glands within three seconds. All the evidence supports the view that the response is mediated by a branching axone system and thus resembles the pilomoter response described by Lewis and Marvin (1927). The fibres mediating the response lie in the skin, as the response is stopped by intradermal novocain. It may also be deduced that they are very small fibres from the fact that they are relatively immune to compression and have a low optimum frequency of stimulation.

The spread of the response is of some interest, as its analysis may give a clue to the arrangement and distribution of the terminal filaments of the sympathetic nerves. The fact that one gland may be stimulated from several different points might suggest that each individual gland has a multiple innervation. This is improbable because of the large number of nerve endings which would be required. Another explanation is the presence of a peripheral plexus or interlacing network of nerves. Such a plexus fails to explain why the response does not pass around a wheal of novocain.

Another possibility, better supported by the experimental evidence, is that not one but numerous interdigitating branched axone systems are being stimulated. It is suggested that the sympathetic fibres innervating sweat glands divide near their terminations into many fine filaments which radiate through the skin in all directions. Each such ramification may be called an axone system. These axone systems overlap each other to a very considerable extent, and at any given point in the skin many axones belonging to different systems are present. It is evident that an axone system which has its centre near the site of stimulation will be much more likely to supply a fibre passing this point than one which has its centre further away. This conception would fulfil the following requisites. Stimulation at a single point would activate the majority of the glands close to the site of stimulation. As the axone systems supplying the glands lying at the periphery of the response would not all be represented at the point of stimulation, only such as are there represented would respond. The glands at the periphery which did respond would usually do so later and less intensely than those near the stimulus, because the axone systems supplying them would be less likely to receive the full force of the stimulus than the axone systems whose fibres are concentrated at that point. Stimulation at one point on repeated occasions would give consistent responses. Stimulation at many different points along the one axone system would always cause a given gland to secrete. A very small wheal of novocain would not entirely block the passage of impulses to the glands on the other side of it, while a larger wheal would do so. It would not matter to which side of the novocain the stimulus was applied. By the simple modification of making each axone system extend over a narrower and more elongated area the shape of the response on the forehead and foot would be explained. Inasmuch, therefore, as this theory fits all the observed facts it is suggested as a probable representation of the actual conditions present. If this be granted, it may be deduced that the diameter of an axone system is equal to the radius of the response. There must, however, be considerable variability in the length of the terminal radiating filaments to account for the outlying groups of glands which may be activated.

SUMMARY.

A local sweat response to faradic stimulation of the skin has been described.

It depends on a local axone reflex mediated by the post-ganglionic sympathetic fibres.

Many overlapping axone systems are involved.

The authors wish to express their gratitude to Professor J. Paterson Ross for making available the subjects on whom sympathectomy had been performed, and to Dr. E. Arnold Carmichael, under whose direction the work was carried out.

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DISSEMINATION OF A GLIOMA OF THE SPINAL CORD IN THE LEPTOMENINGES.[1]

BY KENNETH C. EDEN.

SINCE Ollivier (1837) first described the condition a number of cases of so-called "primary diffuse sarcomatosis of the cerebral and spinal meninges," have been described. The later discovery of neuroglial fibres in such new formations led Pels-Leusden (1898) to employ the term gliosarcoma. When the difference between sarcoma of connective tissue derivation and glioma arising from the central nervous system became clear, this self-contradictory term was abandoned.

More recently, Bailey and Cushing (1925) were able to show that the mid-line cerebellar glioma, medulloblastoma, of children displayed a tendency to spread in the leptomeninges and was not uncommonly responsible for such dissemination.

Subsequently, Cairns and Russell (1931) and others reported examples of metastasis in the case of other varieties of glioma.

The present paper records and discusses a case of generalized leptomeningeal dissemination, showing many of the features of primary meningeal sarcomatosis, arising from a glioma of the spinal cord.

The patient was a man aged 19, a hairdresser, admitted on August 28, 1936, to University College Hospital under the care of Dr. F. M. R. Walshe. Apart from appendicitis and mastoiditis in childhood he had enjoyed good health until the onset of the symptoms now to be described. Seven weeks before admission to hospital he began to notice a sensation of "pins and needles," first in the right, and within a few days in the left, leg. This was accompanied by numbness and quickly spread up to the thighs. Both legs then began to grow weak, the right before the left, and within a few days both were severely paralysed, movements at the hips being less impaired. There was neither pain nor disturbance of sphincter control.

A course of massage and electrical treatment at another hospital effected a temporary improvement, so he thought, but the weakness soon increased again.

On examination he proved to be thin and pale, in no pain and with a normal temperature. He was intelligent and co-operative. The mouth, thoracic and abdominal viscera appeared normal. There was an old perforation of the right ear-drum with some deafness of middle-ear type. The fundi and cranial nerves were normal. There was no neck rigidity.

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[1] From the Surgical Unit, University College Hospital.

The legs were paralysed, except for feeble movement at the hips. The abdominal muscles were normal.

All forms of sensation were severely impaired below the middle of the thighs anteriorly, and below the lumbosacral junction posteriorly. Below the knees postural and vibration sensibility was absent.

The arm-jerks were normal, but the knee and ankle jerks abolished on both sides. The plantar responses were both of extensor type, the abdominal reflexes and the anal reflex were normal.

Kernig's sign was absent.

Lumbar puncture revealed an incomplete block, with an initial pressure of 250 mm. water, and a slow rise and delayed fall on jugular compression. The fluid was clear and yellow in colour. It contained two cells per c.mm., an increased globulin content, chlorides 0·73%, sterile on culture. In the blood the hæmoglobin content was 106%, colour-index, 0·92, R.B.C.s 5,850,000, W.B.C.s 6,400, and polymorphonuclear cells 64%. The Wassermann reaction was negative in both blood and cerebrospinal fluid. A radiogram of the spine revealed no abnormality.

On September 29, cisternal puncture, and lipiodol (2 c.mm.) injection were performed. The theca punctured easily, but there was some difficulty in introducing the lipiodol, and during the procedure the patient collapsed and vomited several times. A radiogram showed that only a few drops of lipiodol had entered the theca, the rest having passed extrathecally.

Clinical Course.

During the night of October 10 he suddenly complained of pins and needles in both arms, developed complete dysarthria and vomited repeatedly. A few hours later he was able to say "Yes" and "No," but otherwise his speech was unintelligible. Next day the speech had improved, but there was loss of power of protrusion of the tongue, slight weakness of the right arm and leg and the lower right face. Shortly afterwards he developed severe headaches, vomiting, and diplopia, with a left external rectus weakness. This all cleared up during the next week, but he then began to have difficulty in micturition and developed retention of urine. The urine contained pus and red cells and a culture grew *Bacillus coli.* From then onwards he was catheterized twice daily with regular bladder washouts of 2% mandelic acid.

On October 16 he was transferred to the Surgical Unit Ward. The squint, facial palsy and weakness of the right arm had disappeared completely. The paralysis and anæsthesia of the legs were unchanged but spasticity was becoming marked and flexor spasms could be elicited readily by pin-prick on either leg. There was a subjective sensation of "pins and needles" in the buttocks and front of the thighs, but no area of hyperæsthesia could be found.

Laminectomy was performed by Mr. Wilfrid Trotter under general ether anæsthesia on November 24. The spines and laminæ of the 11th and 12th dorsal and 1st and 2nd lumbar vertebræ were removed. The dura appeared to bulge under tension and was opened. The arachnoid was thickened and the cauda equina matted. No definite gelatinous exudate was observed at operation. The lower part of the lumbar enlargement and conus medullaris were uniformly expanded and were considered to be the site of an intramedullary tumour. No attempt was made to remove it, the dura was left open and the wound closed.

At the end of a week sensation in both legs had improved very slightly and firm pressure was just appreciated after a delay. He then began to complain of failing vision at this time and examination revealed two dioptres of papillœdema in the right eye and a distinct temporal pallor of the left disc. His hearing, which had always been poor, also deteriorated and a moderate degree of nerve deafness was discovered in the left ear in addition to the chronic middle-ear deafness on the right side associated with an old perforation. He had three large bed sores on the buttocks which were proving very resistant to treatment. Early in December he became incontinent of urine and fæces, which persisted from then until his death on January 26, 1937. He became gradually more drowsy and incoherent, with a

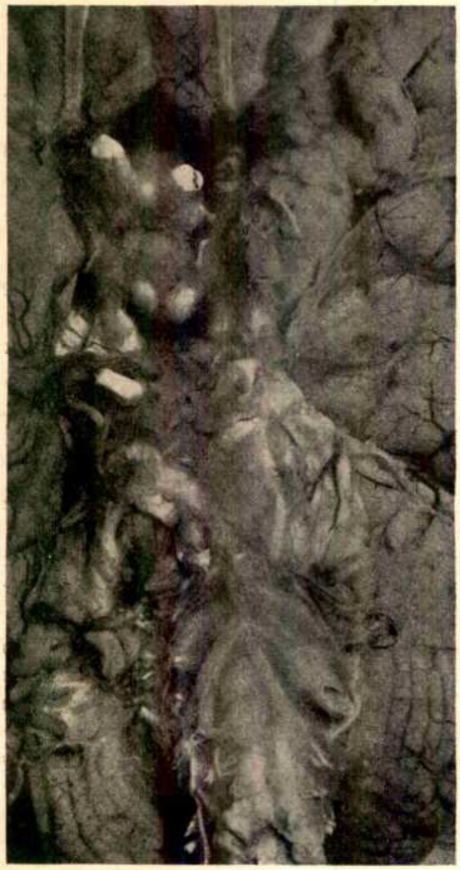

FIG. 1.

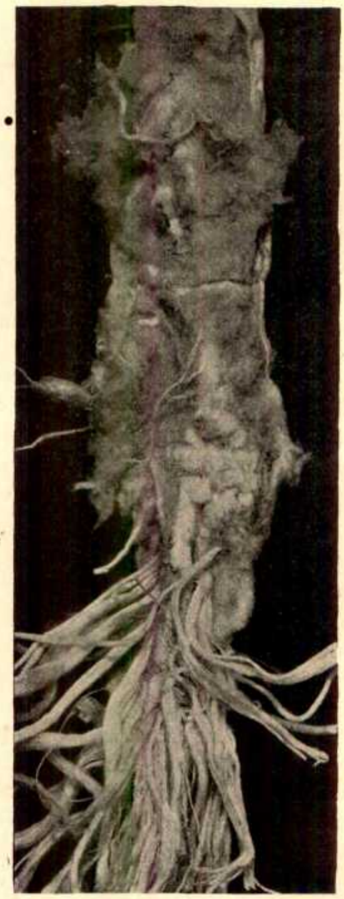

FIG. 2.

FIG. 1.—Base of the brain, showing tumour lying in basal cisterns and surrounding infundibulum, and spread over brain-stem, cerebellum and temporal lobe.

FIG. 2.—Dorsal aspect of lower thoracic of lumbar and sacral regions of cord, showing the diffuse leptomeningeal infiltration by tumour.

great deal of vomiting, confused articulation and wandering of the mind and there were two attacks of generalized convulsions lasting a few moments and accompanied by a loss of consciousness, neck retraction and twitching of all the limbs.

AUTOPSY EXAMINATION PERFORMED BY PROFESSOR G. R. CAMERON ON JANUARY 27, 1937.

The subject was a pale, emaciated man with a healed laminectomy scar in the lumbar region and three large unhealed bed sores, one over the sacrum and two on the buttocks.

Brain.—The dura mater was everywhere intact and normal. The arachnoid was tensely distended by a gelatinous, pinkish-grey exudate. This was least marked over the cerebral hemispheres, but very dense at the base of the brain. The infundibulum and optic chiasma were partially buried in a thick, gelatinous mass of tumour which filled the interpeduncular space and largely obscured the circle of Willis and the origins of the cranial nerves (fig. 1). The pons and medulla were surrounded by growth. A thin film of tumour spread out in the leptomeninges over the surface of the cerebellum and along the sulci of the temporal lobes. The ventricles were moderately and uniformly dilated but no definite tumour masses were detected. The exudate could be traced as a thin layer along the floor of the 4th and 3rd ventricles into the right lateral ventricle but not into the left. Careful sections of the cerebellum revealed no trace of a primary tumour and a similar investigation of the whole of the remainder of the brain was negative.

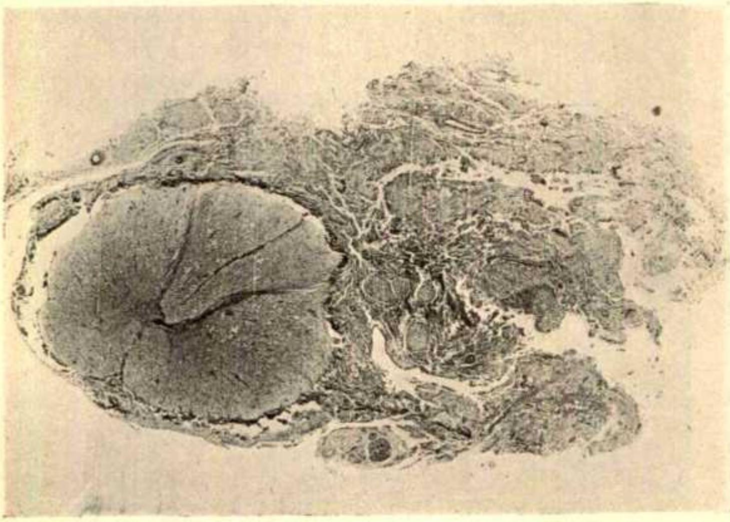

FIG. 3.—Cross section of thoracic region of cord, showing a cuff of tumour. (× 6. van Gieson stain.)

Spinal cord.—The dura was uninvaded but tensely distended by the tumour. The pia-arachnoid throughout the length of the cord was replaced by gelatinous tumour (fig. 2). This was most marked on the posterior aspect and the right side and continuous with the infiltration at the base of the brain. In the dorsal region the cord was displaced to the left by the dense accumulation on the right side (fig. 3). The origins of the nerve roots were partially hidden and surrounded by a cuff of tumour as they entered their dural sheaths. In the lower part of the lumbar enlargement the outline of the cord, which everywhere else was quite distinct, was indefinite and the cord was replaced by an irregular pinkish-grey tumour continuous with the growth in the leptomeninges. The cauda equina was densely matted and studded with nodules of soft irregular growth.

Other organs.—The tongue, mouth, pharynx, tonsils, salivary glands and œsophagus were all normal ; the stomach contained a little mucus and brownish fluid and showed a few scattered submucous petechiæ. The intestinal tract was normal. The heart and aorta showed no abnormality. The lungs were healthy except for a few old pleural adhesions and the bronchi contained only a little mucus. The liver, gall-bladder and spleen were healthy, the bladder contracted and congested with signs of acute inflammation and hæmorrhages, most marked over the trigone. The prostate, vesiculæ seminalis and testicles were normal. The suprarenal glands were of average size and showed no tumour deposits. The thyroid was pale yellow and of normal size. Both eyes and orbits showed no growth.

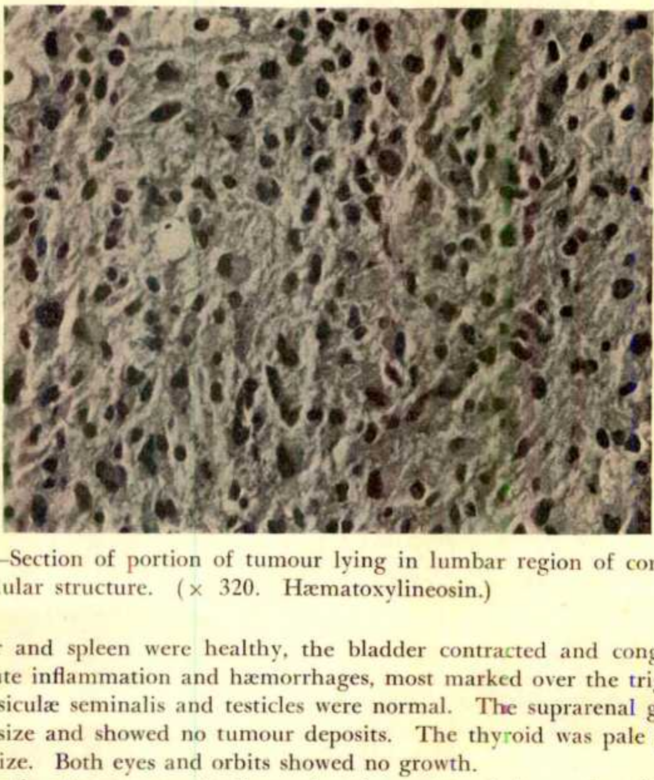

FIG. 4.—Section of portion of tumour lying in lumbar region of cord, showing general cellular structure. (× 320. Hæmatoxylineosin.)

Microscopic appearances.—Sections of various parts of the cord and brain were stained with hæmatoxylin and eosin, van Gieson, Mallory's connective tissue stain, Mallory's phosphotungstic acid hæmatoxylin, Perdrau's silver impregnation for reticulum and Wilder's silver impregnation for neuroglial cells and nerve cells.

Sections through the lower lumbar region of the cord showed invasion throughout by cellular tumour (fig. 4). In places recognizable spinal cord substance could be detected although the delineation of grey and white matter was completely destroyed. Elsewhere the mass consisted of a densely cellular tumour continuous with an infiltration of the leptomeninges. The vasculature was very rich, consisting mainly of numerous branching arterioles with fairly well-formed walls. In places they were somewhat varicose. There was no endothelial proliferation or hyalinization of the walls and no areas of necrosis were present in the tumour. By Perdrau's method the blood-vessels showed up clearly with a small amount of connective tissue around them and only a little reticulum scattered in between. In sections stained by hæmatoxylin and eosin the cells showed a great variation in size and configuration. The commonest type was one with a round or oval nucleus deeply hyperchromatic, with dense chromatin particles scattered throughout the nucleus. In some cells the chromatin was so dense that no structure could be made out in the nucleus. The cytoplasm was irregular and poorly stained. Many of the cells resembled large and small astrocytes with typical oval nuclei of medium size and scattered chromatin and swollen, badly-stained, branching cytoplasm, the nucleus very often being pushed to one side. In addition there were a considerable number of cells resembling spongioblasts. The nuclei of these cells were very large and hyperchromatic, often multiple or bilobed with cytoplasm forming one or two branching processes.

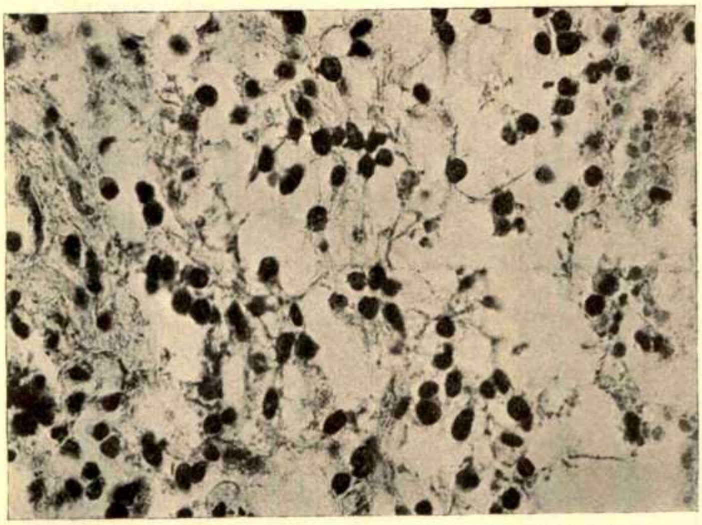

FIG. 5.—Tumour showing neuroglial fibres. (× 500. Mallory's phosphotungstic acid hæmatoxylin.)

Leptomeningeal

Here and there in the remnants of cord substance a few nerve cells could be picked out, all in various stages of degeneration and many with swollen and hydropic cytoplasm. In preparations stained with phosphotungstic acid hæmatoxylin, neuroglial fibres were fairly plentiful, forming a network throughout the tumour (fig. 5). One or two centrosomes could also be made out. Occasional mitotic figures were present but they were not very pronounced. With silver impregnation preparations the majority of cells were large and irregular with one or more branching processes, some of them frayed at the ends. Only one or two sucker processes were found. Large and small astrocytes, unipolar and bipolar spongioblasts were all readily identifiable.

Elsewhere in the cord the leptomeninges were densely packed by cellular infiltration invading the sulci and surrounding the blood-vessels and nerves but not extending into the substance of the cord. A thin layer was also present over the entire cortex invading the cerebral sulci and Virchow-Robin spaces but not spreading into the subcortical white matter. With van Gieson preparations a well-marked fibroblastic reaction was shown to be present, mostly adjacent to the cord and around the blood-vessels and nerves but also scattered irregularly throughout the infiltrating tumour. Among the bundles of collagen fibres the more elongated spindle-shaped vesicular nuclei of the connective tissue cells were readily distinguishable from the invading tumour cells. With Perdrau's method the reticulum was seen to be scattered irregularly in a radial manner between the blood-vessels without any concentric ring formation but was a little more plentiful adjacent to the blood-vessels than elsewhere (fig. 6). The striking characteristic of the tumour infiltrating the leptomeninges as compared with the tumour in the cord was the comparative uniformity of the cells. In preparations stained with hæmatoxylin and eosin there was a great preponderance of the smaller cell type with a few spongioblasts scattered throughout. Mitoses were rather few. Phosphotungstic acid hæmatoxylin preparations showed a network of neuroglial fibrils. In most of the cells few processes were distinguishable with the silver impregnation method but here and there were small astrocytes and spongioblasts. The large astrocytes were much more infrequent here.

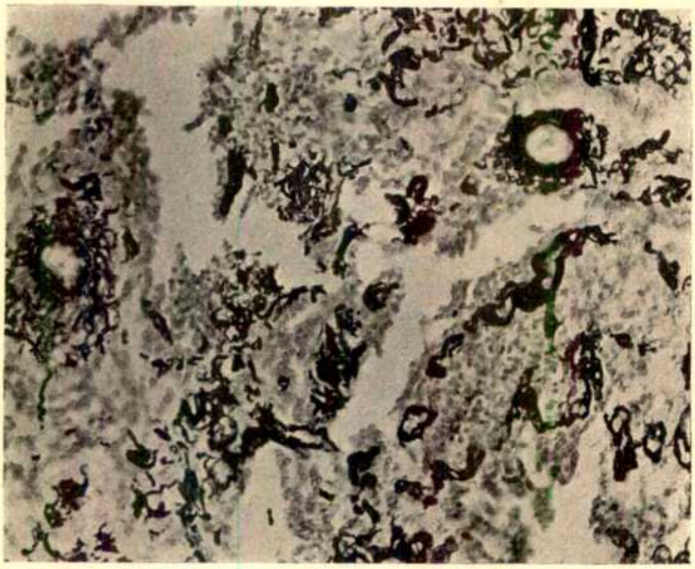
FIG. 6.—Leptomeningeal tumour, showing fibrous tissue and reticulum. (× 120. Perdrau's method.)

The multicellular character of this tumour makes it difficult to place it in any of the usually accepted classifications of gliomas. Its cellular character suggests its inclusion amongst the glioblastoma multiforme group, but the lack of degenerative and characteristic changes in blood-vessels seems rather to weigh against this. It is therefore best regarded as a mixed-cell glioma of uncertain nature.

DISCUSSION.

The capacity of gliomas to metastasize by way of the cerebrospinal fluid was not recognized until comparatively recently. Such metastases had not been recorded elsewhere in the body and the glioma was regarded as a tumour of purely local invasive character.

Recorded examples of diffuse formation of tumour in the leptomeninges had therefore been looked upon as a primary diffuse sarcomatosis. Later, with the improvement of methods of staining, neuroglial fibres were detected in such tissue.

Ford and Firor (1924) published a case of gliomatosis of the leptomeninges and listed nine other cases from the literature. It was only when Bailey and Cushing described the clinical and pathological features of the mid-line cerebellar medulloblastoma in children with dissemination in the leptomeninges that it began to be possible to classify these tumours. They were able to show that a large number of the cases described in the literature as diffuse tumours of unknown origin, were in reality examples of this condition. These included the original case of Ollivier, several of the cases discussed by Ford and Firor, and many others. Since then further examples of dissemination by other types of glioma have been recorded, although no other tumour has been shown to manifest the same readiness to spread in the leptomeninges as the cerebellar medulloblastoma. Cairns and Russell's group of cases showing intracranial and spinal metastases in gliomas included in addition to further examples of cerebellar medulloblastomas, instances of neuro-epithelioma of the retina, glioblastoma multiforme, astrocytoma and ependymoma. They concluded from their observations on twenty-one consecutive full autopsies in cases of glioma, in which eight showed spinal metastases, that the frequency of this process is much greater than had been supposed.

The instances of dissemination of spinal tumours are very few in the literature. Frazier (1918) stated that pure intramedullary spinal tumours are limited to the cord itself and never invade the meninges. Kernohan (1932) was only able to give one example and that was of an oligodendroglioma of the cord which was exposed at operation and decompressed by a vertical posterior incision into the cord. At autopsy the tumour was found to have spread upwards and downwards for a short distance in the leptomeninges with a well-marked fibroblastic reaction. Elsberg (1925) described no examples of dissemination of tumours of the cord, but emphasized their tendency to extrude themselves and grow out of the cord substance. Grund (1906) recorded a case of a large intramedullary tumour of the cervical spinal cord with infiltration of the adjacent leptomeninges and Rutimeyer

(1930) described an intramedullary tumour in the lower part of the cord which had spread up as far as the cervical cord. Professor Forster has very kindly allowed me to refer to an instance in his extensive series of spinal tumours which he will discuss in his book on tumours of the brain and spinal cord. This was described as a medulloblastoma of the lumbar cord in a young woman aged 29, which spread throughout the subarachnoid space of the spinal cord, base and convexities of the brain. In the case recorded by Pels-Leusden of compression of the lumbar cord by a tumour mass with diffuse dissemination in the leptomeninges which he described as a gliosarcoma, there was a mass of growth in the left lateral ventricle which it is impossible to exclude as the primary tumour.

There remain a number of cases in which after detailed examination no primary tumour has been discovered in the central nervous system. According to Willis (1934) some of these cases are due to carinosis. In his opinion the case of diffuse tumour spread described by Olivecrona (1914) is an example of this condition. Nodules of growth were found in several of the viscera, one of which might have been the primary growth. In addition some of the diffuse leptomeningeal growths have been pigmented and small unrecognized melanotic growths of the skin or the eyes may have been overlooked. In other cases in which these primary sources have been eliminated it seems possible that the growth may have originated in areas of pigmentation in the central nervous system. Masson (1926) believes that the presence of pigment is indicative of an ectodermal rather than a mesodermal origin and this is significant in view of Harvey and Burr's (1926) conclusions that the meninges are really of ectodermal origin.

The existence of true diffuse primary sarcomatosis of the leptomeninges is somewhat doubtful. Bailey (1929), however, still believes that it exists as a definite pathological entity with characteristic features. He points out that there are cases of diffuse leptomeningeal growth in which no primary tumour has been found and that in contradistinction to the medulloblastomas of children they occur in adult subjects. They originate by a sarcomatous transformation of the perivascular sheaths—" the peritheliomas "—which may be distinguished from gliomatous invasion of these sheaths by the intact pia-glial membrane in the latter. The cells in these tumours, he says, tend to be arranged in cuffs around the blood-vessels, often several cells thick and the reticulum is plentiful and distributed in concentric rings around the blood-vessels. The infiltrating gliomas may contain reticulum, but it is more scanty and irregularly arranged in a radial manner between the vessels. Moreover the nuclei of the connective tissue in the leptomeningeal gliomas may be clearly picked out from the glial cells, whereas in the peritheliomas only one type of cell is present.

The possibilities which were considered in the case under discussion were that it was a case of primary sarcomatosis of the meninges, a disseminated cerebral glioma invading the lumbar cord, or a spinal glioma with leptomeningeal spread. The latter explanation was held to be the only tenable one in view of the evidence. Clinically the paraplegia marked the onset of symptoms and predominated throughout in spite of the subsequent scattered signs elsewhere in the nervous system. At operation the lower lumbar and sacral cord was seen to be enlarged and thought to be the seat of an intramedullary tumour, but no disseminated tumour was then observed. The autopsy revealed no primary tumour in spite of careful search in the nervous system or elsewhere, but a mass of gliomatous tissue was found replacing the lower part of the cord. The microscopic examination revealed the fact that the cells invading the leptomeninges were glial in origin and distinct from the connective tissue cells which lay in relation to the fibroblastic reaction. The reticulum was scanty and irregular in distribution. The difference in the cellular structure of the primary tumour in the cord and the leptomeningeal infiltration was thought to depend on the nature of the tissue invaded, the fibroblastic reaction and the predominance of the smaller cell type occurring in the meninges and the densely cellular structure with large numbers of spongioblasts characterizing the primary tumour.

It is not clear why certain gliomas show a marked tendency to spread in this manner and others do so only rarely. The most important single factor would seem to be the nature and degree of malignancy of the tumour. The position of the tumour in close relationship to the ventricles or cisterns naturally is of importance. However, very many tumours impinge on the subarachnoid space without apparently giving rise to any metastases, although Cairns and Russell's observations indicate that the frequency may be greater than is thought. Operative interference has also been thought to play a part by the scattering of cellular emboli in the cerebrospinal fluid and the opening of deep-seated tumours to the subarachnoid space. The natural tendency of the cerebellar medulloblastomas to disseminate is such that the role of operative interference in these cases is very difficult to assess. Kernohan's case of oligodendroglioma of the cord which was incised with subsequent leptomeningeal infiltration, would seem to suggest that the exposure of the tumour substance to the cerebrospinal fluid determined the dissemination. In the case described in this paper, however, the cord was not incised and it is probable that dissemination had already begun before the operation.

Examination of the recorded cases indicates two types of metastases in gliomas. In a variety of tumours scattered nodules have been observed on the posterior aspect of the cord, at the base of the brain and in the floors of the ventricles. The supposition is that cellular emboli are thrown off from the tumour into the cerebrospinal fluid, are carried into the perivascular spaces and settle in the dependent part under the influence of gravity. Some of these emboli continue to grow and form secondary nodules of growth in the leptomeninges. The other type of spread is an apparently continuous permeation of the tumour throughout the leptomeninges. It is doubtful, however, if this process can be compared with lymphatic permeation. Gravity seems to play an important part here, too, and it is probable that in reality the same mechanism is involved but on a much larger scale than in the formation of nodular metastases. In the case described although there was a thin continuous layer of infiltrated tumour throughout the leptomeninges, the main accumulation was in the dependent parts. The patient lay throughout his illness on his back and right side and the tumour was found distributed most densely on the posterior and right sides of the cord, the base of the brain and in the right lateral ventricle, but not in the left.

The clinical picture of leptomeningeal dissemination of tumours is in no sense clear cut. Ford and Firor attempted to classify the cases into definite clinical types, but were confused by the various types of cases included. It is clear that the signs of dissemination may be superimposed on those of the primary tumour, as in the case described, or the primary tumour may pass entirely unnoticed. On the other hand a distinct interval may be present before dissemination is manifest, as occurred in a case of cerebellar medulloblastoma treated at this hospital by a posterior fossa decompression and X-ray therapy to the brain. All the signs of a tumour of the posterior fossa cleared up rapidly and the girl was able to get about quite normally for three months, after which she developed a paraplegia and died of generalized tumour dissemination. Winckelman and Eckel (1936) described a case in which the primary tumour of the cerebellum was actually removed and the patient was free from symptoms for two years before the onset of spinal invasion.

The variability of the clinical course with periods of exacerbation and remission which was manifested by the case described is very characteristic and has been noted by many writers. The cisternal puncture with alteration of the intracranial pressure disturbed the patient profoundly and it is probable that the difficulty in introducing any lipiodol inside the theca was due to the presence of tumour at that time in the leptomeninges. It is very difficult to understand why the isolated palsies which developed some days later should have cleared up completely. The complete absence of root pains is also a well-established characteristic, and was thought by Winckelman and Eckel to be due to the soft nature of the infiltrating tumour. It is remarkable that although the leptomeninges were infiltrated throughout with tumour, the only permanent signs until very late were those of the primary cord tumour. This must be attributed to the absence of invasion of the nervous system except in the lumbar cord. The signs of raised intracranial pressure only developed to a severe degree in the last few weeks of his illness when the subarachnoid space was presumably dammed up. Meningeal signs were very inconspicuous throughout, although they might reasonably have been expected to predominate. The analysis of the cerebrospinal fluid should be of crucial importance in the diagnosis. It is unfortunate that the possibility of diffuse spread was not entertained in this case. Since Forster (1930) has shown that by a careful analysis of centrifuged cerebrospinal fluid in cases of cerebral and spinal gliomas, using special staining methods, it is possible to identify the characteristic tumour cells in a considerable proportion of cases, it should certainly be possible to detect the cells in large numbers in these cases of diffuse dissemination and in any suspected case it is most important to look for the cells.

Once the diagnosis is established the only rational treatment is deep X-ray therapy to the central nervous system, in view of the extreme sensitivity to irradiation of such tumours as the cerebellar medulloblastoma. Our experience in this hospital of a case of cerebellar medulloblastoma with irradiation of the primary tumour which was followed a few months later by spinal subarachnoid invasion, emphasizes the importance of irradiating all parts of the nervous system.

I am indebted to Mr. Wilfred Trotter and Dr. F. M. R. Walshe for permission to review this case, and to Professor G. R. Cameron, Dr. J. G. Greenfield and Dr. L. E. Glynn, for their help in studying the pathology, and to Professor O. Foerster for his kind permission to refer to his case.

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FIBRILLATION AND FASCICULATION IN VOLUNTARY MUSCLE[1]

BY D. DENNY-BROWN AND J. B. PENNYBACKER.

INVOLUNTARY fibrillary twitching of muscle is a phenomenon observed frequently in the course of clinical examination of patients suffering from nervous disorders. It is apparent to the naked eye that what is commonly called "fibrillation" in amyotrophic lateral sclerosis, for example, differs in type from muscle to muscle, and from time to time in the same patient. Of these differing varieties there is little mention in the literature, nor of their relationship to other kinds of involuntary twitching in muscle.

The following study is of myographic and electromyographic records of these various forms of involuntary twitching of muscle fibres.

(1) METHOD OF INVESTIGATION.

The twitching of the muscle has been recorded by concurrent records of the mechanical twitch and the electrical action current of the fibres concerned. The electrical action current has been recorded by inserting a hypodermic needle through the skin into the substance of the muscle being investigated, a superficial portion of the muscle fibre being selected for the purpose. The second electrode in the form of a thin copper wire insulated with cotton winding soaked in celloidin, with silvered perforation at its end, is inserted through the needle just to protrude through its end. Thus the tip of the wire core forms one electrode among the muscle fibres, separated by 1 to 2 mm. from the nearest part of the needle, which forms the other electrode. The wire and the hypodermic needle are connected to the input side of a four stage amplifier leading to a Matthews Oscillograph, of which the galvanometer mirror reflects a beam of light on a strip of moving bromide paper. Over the region where the tip of the hypodermic needle lies in the muscle a small cork button or pyramid is stuck to the skin by collodion. Over the button is a balloon lightly inflated with air, and held by adhesive plaster to the body wall or to a metal guard clamped round the limb. Any mechanical movement of the piece of muscle concerned moves the cork, and produces a fluctuation in the air pressure in the balloon which is transmitted by a short length of pressure tubing to a manometer with mirror diaphragm. The movements of the manometer mirror are recorded by a beam of light which is reflected to the same strip of moving paper as records the action currents. The latency of the mechanical system used was 0·004 sec., i.e. the mechanical record lags behind the electrical record by this time interval. In the animal experiments fibrillation was recorded by a very small steel mirror directly applied to the muscular surface.

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[1] This investigation was made in 1934-35 during the tenure of a Halley Stewart Fellowship by one of us (D.D-B.) in the Research Unit, National Hospital, Queen Square, London.

It cannot be too strongly emphasized that mechanical records made in this manner must be controlled carefully by visual observation of the surface of the muscle.

(2) Interpretation of Observations on Muscular Function.

Inasmuch as it is desired to discuss the relationship of different forms of involuntary twitching to the functional structure of muscle, it is desirable here to outline some anatomical and physiological facts relating to muscle. The unit structure of a muscle is a muscle fibre, a structure which has a diameter in man of from 0·01 to 0·10 mm., and in most muscles a length of 3 to 5 cm. In some exceptional muscles such as sartorius or platysma the length of the fibre may be as great as 12 cm. (Felix, 1887). Muscle fibres in skeletal muscle are independent structures with separate existence, and without syncitial interconnection, as can be demonstrated by teasing methods (Felix, 1887, Denny-Brown, 1929a). They can contract independently (Pratt and Eisenberger, 1919, Gelfan and Bishop, 1932).

Fibres are grouped in natural bundles called fasciculi, each containing many hundreds of parallel muscle fibres in a coarsely fasciculated muscle, such as gluteus maximus, or smaller bundles with less defined edges in pennate muscles such as the extensors of the wrist or the interossei. While a muscle fibre therefore is of a thinness which can just be detected by the naked eye, the fasciculus is a structure of some 2 to 10 mm. in diameter. The functional significance of the fasciculus appears to be its vascular arrangement, with terminal artery and independent veins. That it is not nervous is shown by the common pathological observation that, as a result of lesions affecting only a certain number of fibres in the motor nerve, a portion of a fasciculus may suffer extreme degeneration and the remainder appear healthy (Durante, 1902, Wohlfart, 1935).

Though physiologists have come to regard the muscle fibres as each having dependence upon one nerve fibre, and each motor nerve fibre serving in this way a number of muscle fibres, it has from time to time been asserted that muscle fibres derive motor supply from a plexus to which the total of the motor nerve fibres contribute (Wilkinson, 1931). Modern treatises on anatomy, histology or physiology give the reader no guidance, except to indicate that it has been asserted that muscle fibres receive more than one end plate. It is necessary, therefore, to present as briefly as possible the evidence for the first view, which appears to us to be well founded. The point is of importance to the understanding of the electromyogram as well as of the atrophy of muscle.

Each ordinary muscle fibre in a limb muscle receives one motor end plate. That this is the only end plate can readily be seen in cutaneous muscles or sartorius in the frog as studied by Krause (1869), Kuhne (1884, 1886), Kulchitsky (1924) and others, and with methylene blue staining their finding is readily verified. This arrangement of one motor ending to each muscle fibre has been found also in the silver impregnation staining of limb muscles of the developing mammal (Tello, 1917, 1922) and in sartorius, soleus, tibialis anticus, of the young cat as studied by one of us (D. D.-B.). The exceptions to the rule are the intrafusal muscle fibres of the muscle spindles (Agduhr, 1919), and some very long fibres in pleurisegmental cutaneous muscles such as the panniculus of the hedgehog (Garven, 1925). In the muscles of the tongue several nerve endings may commonly arise from a network of intercommunicating nerve fibres (Boeke, 1911, 1932), but it remains to be demonstrated that this arrangement is other than a persistence of the embryonic neurofibrillar network of a single motor neurone innervating a bundle of contiguous muscle fibres (Tello, 1922). Occasionally very long fibres are found with two end plates in the limb muscle of the frog (Krause, 1869), but these are exceptional and moreover it has not been demonstrated conclusively that the endings seen are not branches of the same parent nerve fibre.

The contraction of the same fibres in flexor communis digitorum in the pig by stimulation of the ulnar or the median nerve by Agduhr (1919), and the radicular innervation of all or nearly all this muscle by both 8th cervical and 1st thoracic nerve roots in this muscle in the rabbit by Lederer and Lemberger (1907) require further investigation, for the phenomenon does not appear compatible with common observation in clinical disorders of this muscle in man. Methods of recording contraction in which the muscle is permitted to shorten are not adequate to decide the point. (See discussion by Fulton, 1926, Chap. VI).

Agduhr (1916, 1919) has described double, and sometimes triple, innervation of muscle fibres of the flexor digitorum sublimis in animals by selective degeneration of the 8th cervical and 1st thoracic nerve roots. The three end plates he pictures are shown lying close together in different stages of degeneration. It is quite unknown for a normal muscle fibre to receive three end plates close together. In paraffin sections by the Bielchowsky method it is notoriously difficult to distinguish one muscle fibre from another just underneath it. For this reason Agduhr's findings cannot be accepted as indicating a general principle until confirmed by other, preferably teasing, methods.

Degeneration of muscle fasciculi following partial section of a motor nerve or nerve-root is partial ; thus groups of muscle fibres degenerate upon section of particular nerve fibres. There are no transitional forms of degeneration, so that muscle fibres do not depend, partially upon some nerve fibres partially upon others, but each upon its own particular motor nerve fibre. A classical example cited in opposition to this general principle is that of the crico-thyroid muscle which is stated by Exner (1885) and Livon (1891) not to degenerate when either one of its component nerve supplies, superior laryngeal, and laryngeal plexus, is sectioned. Exner states that the muscle degenerates if both nerves are sectioned. These observations are so directly at variance with the effect of stimulating the two nerves (Lederer and Lemberger, 1907), and the physiological and pathological findings quoted above, that its repetition with modern methods is highly desirable. Some muscles such as the external anal sphincter (Arloing and Chantre, 1898) are resistant to paralytic atrophy. The degeneration of muscle depends not at all upon sensory nerve fibres, nor is it delayed by their integrity.

Of the two or more nerve roots supplying a muscle, stimulation of one causes a contraction of a different part from that contracted by another (Gad, 1882, Sherrington, 1892, de Boer, 1925-26, Van Rijnberk, 1911) and fatigue of one group of fibres little affects the contraction from the other (Gad, Fulton, 1926, Van Rijnberk, 1929). When one group is already thrown into a fused contraction-tetanus by rapidly repeated stimulation, the other can be made to twitch in more isolated manner (Samojloff and Wassiljewa, 1925), the veratrin contracture of one group can be fatigued without that of the other (de Boer), and lastly the mechanical thermal and electrical effects of isometric contraction each of two such groups of motor fibres to a muscle can be summed almost exactly by combined stimulation of both motor roots together (Samojloff, 1924, Samojloff and Wassiljewa, 1925, Fulton, 1926).

From all these different points of view it may be concluded that each muscle fibre depends upon one nerve fibre, and therefore one motor anterior horn cell. Since the motor nerve to a muscle contains many fewer motor-nerve fibres than there are muscle fibres, and nerve fibres can be observed in stained preparations to branch in their course in muscle and supply many muscle fibres, it follows that one motor-nerve fibre supplies a whole and particular group of muscle fibres. This group is found by calculation (Clark, 1930) to average for instance some 150 muscle fibres for soleus in the cat (total 30,000 fibres) and in contraction to be responsible for only 10 gr. of maximal tension (Eccles and Sherrington, 1930). This motor-nerve fibre, its parent anterior horn cell, and its dependent group of muscle fibres have been termed the "motor unit" (Liddell and Sherrington, 1925, Sherrington, 1929, 1931, Eccles and Sherrington, 1930). Such a group can be observed to contract alone in an all-or-none manner in response to excitation of its motor nerve fibre (Pratt and Eisenberger, 1919, Pratt, 1925).

The action currents of a single motor unit in mammalian muscle have been recognized to have each a particular shape, and the discharge of a motor unit can be recognized in the electromyogram by the repetition of a regular shape of action current in series, producing a contraction tension of some ten grams only (Denny-Brown, 1929*b*, fig. 16). This demonstration of the function of a single motor unit was further amplified by Eccles and Sherrington (1930). The electromyographic appearance of the rhythmical electrical discharge has since become well recognized (Adrian and Bronk, 1929, Eccles and Hoff, 1932, and in human muscle by Smith, 1934, Lindsley, 1935-6). The diphasic variation which constitutes the action current of a group of muscle fibres alters in shape according to the disposition of the fibres in relation to the two points of the electrodes which sample the electrical change. The more truly the fibres lie across the two electrodes the more the electrical fluctuation approaches a simple diphasic variation. The closer to the electrode the larger the electrical change that is sampled. Thus each group of muscle fibres belonging to one motor unit lies in a particular position in relation to the points of a needle or other electrode inserted into the muscle, and a wave of contraction in them has a particular shape of electrical action current.

(3) THE FINE FIBRILLATION OF A MUSCLE COMPLETELY DEPRIVED OF ITS NERVE SUPPLY.

Denervated mammalian muscle has long been known to exhibit a fine tremor of its surface. (Schiff, 1851, Langley, 1915-16*c*, Langley and Kato, 1914-15). Usually the tremor is so slight in degree that it is well seen only when the bared surface of the muscle is observed in reflected light. The surface of the muscle is observed to be rippled by a restless agitation without either apparent rhythm or obvious centre of activity. The whole muscle is involved in a confusion of very small twitches. Such fibrillation is related in some way to the wasting following denervation. In the frog, where denervated muscle wastes only very slowly, fibrillation does not occur. (Langley, 1915-16*c*). This phenomenon is most easily observed in man in the tongue when that organ is subject to paralytic atrophy, for here the superficial situation of muscle fibres and thinness of covering facilitate its observation. Where the skin and subcutaneous tissue are thin it can be observed in other skeletal muscles, particularly as a result of damage to peripheral nerves or degeneration of motor anterior horn cells as in poliomyelitis or syringomyelia.

The faint, confused agitation of the surface of the muscle is accompanied by a very fine rapid electrical fluctuation of which a characteristic instance is shown in fig. 1, taken from the mylohyoid muscle of a patient suffering from syringomyelia, with wasting and fibrillation of one half of the tongue and hyoid muscles. These action currents are much smaller than those accompanying motor nervous activity (cf. fig. 11 at the same amplification) and are of such size that they may be each due to the electrical variation of a single muscle fibre.

We have sought to examine this phenomenon further by experimental means by sectioning the sciatic nerve in cats under general anæsthesia, and examining the calf muscles at different periods after the nerve section. For this purpose the animal was decerebrated under deep anæsthesia, after the lapse of an appropriate time interval. The anæsthesia was then allowed to pass off[1] and two hours later the muscle concerned was exposed by skin incision, observed by reflected light, and the electrical record of its action currents made. Langley and Kato (1914-15) have established the onset of fibrillation in denervated muscle of the cat on the fifth day after nerve section and we have confirmed this finding. For the first four days following nerve section no fibrillation is observed in the denervated muscle. Its first appearance is in the form of scattered single and very small momentary indentations of the surface of the muscle. Each is accompanied by a single very small diphasic action current (fig. 2). The electrical change is from 1 to 3 microvolts, but this value is purely relative with needle electrodes. Each twitch can be observed, both by the eye and in the electrical record, to recur at intervals of about two seconds. Fibrillation differs not at all in red and pale muscle fibre in the cat (fig. 3), as also was noted by Langley and Kato (1914-15). These colour differences, which have been found to be concerned with muscular functions other than the contractile process, (Denny-Brown, 1929*a*) are not affected by the atrophic process until its later stages. When the whole belly of a muscle such as soleus in the cat is observed each indentation is seen to be a momentary tightening in the whole length of a very small part of a muscle fasciculus. It would appear to be the repeated twitching of a single muscle fibre with accompanying very small action current at intervals of two to ten seconds (cf. fig. 2). Fascicular twitching does not occur.

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[1] The operation and subsequent decerebration were performed by one of us (D.D-B.) in the department of the Research Unit, the National Hospital. We are grateful for the facilities allowed us by Dr. Carmichael for this purpose.

On the fifth and sixth days few fibres are twitching in this way, and the twitching appears to be confined to those few, the remainder being inactive. Thus only one fibre in a fasciculus may be concerned. On the seventh and later days all fibres are found to have entered upon this phase of recurrent isolated twitchings, and continue to twitch until the muscle is in an advanced state of wasting (fig. 3). We have not attempted to trace the termination of the process. Langley and Kato (1914-15) observed it up to seventy-one days from time of nerve section.

It is readily ascertained by direct visual observation of the surface of the muscle that the twitches in different fibres have no relationship to each other, the one fibre twitching at a particular rate quite independently of those near or far away. The twitching is inco-ordinate. The final state of confused agitation and the confused action currents of fully developed fibrillation are therefore the result of the combined effect of the irregular mechanical and electrical disturbance in thousands of individual muscle fibres (fig. 3). In this state it is occasionally possible to observe that one particular twitch or action current is being repeated at intervals of about two-fifths of a second (fig. 3*b*). Grouped twitching does not occur until drying or mechanical factors intervene. The electrical action currents become more feeble as the muscle becomes more atrophied.

The appearance of the phenomenon of fibrillation after denervation is associated with the development in degenerating mammalian striped muscle of a particular sensitivity to acetylcholine on the fifth day after denervation, as described by Frank, Nothmann and Hirsch-Kauffmann (1922). The muscle may then enter a spasm of contraction on exposure to an extreme dilution of acetylcholine. Afferent nerve fibres, identical with antidromic vasodilators, distributed in muscle (Hinsey and Gasser,

1930) can by antidromic action liberate a contracting substance, probably acetylcholine, although it is not inhibited by atropine (Frank, Nothmann and Hirsch-Kauffmann, 1922, and Dale and Gaddum, 1930), but fibrillation and atrophy continue in the absence of any sensory or sympathetic innervation. On the other hand, the presence of remaining sensory and sympathetic innervation does not materially alter the process of atrophy in animal experiment (Sherrington, 1894) or in the process of disease in man (poliomyelitis).

It was at first thought that the contracture produced by acetylcholine was not accompanied by action currents (Riesser and Steinhausen, 1923). Schäffer and Licht (1926) and Brown (1937) have found that the contracture is accompanied by fine action currents and have noted that the drug enhances fibrillary contractions. Brown has shown that these small action currents appear with smaller doses, and with a large dose the contracture lasting five to ten seconds occurs, and that this phenomenon is free from action currents. It therefore appeared possible that natural fibrillation may be due to natural acetylcholine.

We observed that a drop of saline containing acetylcholine, diluted 1 : 500,000, allowed to fall on the surface of a muscle just commencing to fibrillate on the seventh day after nerve section, brought about an immediate local contraction lasting some twelve to twenty seconds (fig. 4*b*). As the contraction subsided all the muscle fibres in this area remained fibrillating for many minutes, and gradually the disturbance passed *by imperceptible transition* of moderate fibrillation into the original state of a few isolated fibres fibrillating (fig. 4*c*). Acetylcholine contracture appears therefore to be an intense contraction process of the same essential nature as the phenomenon of fibrillation. It therefore appears likely that true fibrillation is due to the sensitization of the denervated muscle fibre to the small amounts of acetylcholine in the circulating blood. In this connection it is of interest that Langley and Kato (1914-15) noted that physostigmine (eserine) markedly enhances fibrillation in denervated muscle, but was without effect before the fifth day. In view of the effect of eserine in inhibiting the natural destruction of acetylcholine in the tissues this observation strongly supports our contention that the fibrillation from acetylcholine is not only indistinguishable from spontaneous fibrillation but is identical with it.

Langley and Kato (1914-15) further observed that a different, coarser, twitching is caused by eserine in the *normal* mammalian nerve-muscle preparation. This, they maintained, is really fascicular, each a twitch in many muscle fibres co-ordinated by a nerve fibre, for this type disappears twenty-nine hours after nerve section, at the time that excitation of the divided nerve first fails to reach the muscle (Langley and Kato, 1914-15, Titeca, 1935). Curare abolishes this effect of eserine. Titeca (1935) has shown that the excitability and conductivity of the nerve begins to wane only on the third day following section, and he places the first point of failure of transmission at the end plate where signs of degeneration begin to appear at the end of twenty-four hours (Huber, 1900, Boeke, 1911, 1921). Therefore it appears necessarily to follow that in the normal nerve-muscle preparation eserine acts on the nerve fibre or nerve fibre termination, but not on the receptive substance or muscle fibre. Acetylcholine also produces similar twitchings in normal muscles (Bender, 1938) with previous injection of a small dose of eserine. The gap of four days in which acetylcholine and eserine fail to stimulate muscle after nerve section would appear to us to be strong argument against the former being the normal transmitter between nerve and muscle.

Langley (1915-16*b*) considered this eserine fasciculation to be an enhancement of a similar phenomenon observable in normal muscle at a certain stage of fatigue, a phenomenon in the light of recent knowledge also possibly attributable to accumulation of acetylcholine near the nerve fibres, but he did not take steps to exclude polarization of electrodes. Until the latter can be excluded it is not possible to decide this point.

Bender (1938) has observed transient contracture of the denervated facial and ocular muscles in monkeys, induced by fright, and the enhancement of this reaction by eserine. This indicates that free acetylcholine can be present in the general circulation, for adrenalin and other substances do not produce the effect. The animals were observed intact, so that true fibrillation could not be seen. The gradual indistinguishable transition we have described from acetylcholine contracture to fibrillation indicates, in our view, that the latter is only a very mild degree of the former, and that smaller amounts of the substance must be present in the normal circulation.

We would conclude, therefore, that the fibrillation of muscle undergoing atrophy as a result of denervation is due to periodic rhythmical twitch excitation of each muscle fibre sensitized by neural atrophy. The source of the excitation would appear to be the small amounts of acetylcholine in the normal circulation. We would refer to this phenomenon as "true fibrillation," to distinguish it from other more coarse varieties of muscle twitching to be mentioned below. Such true fibrillation occurs in all voluntary muscles deprived of motor nerve supply. From observations on wasting muscles resulting from diseases affecting motor neurones it would appear that intact sensory nerves to muscle do not influence the phenomenon. In most patients with wasted limb muscles from neuritis or poliomyelitis this fibrillation cannot be observed by clinical examination. When, however, the subcutaneous tissue is unusually thin these muscles can be seen to present the fine characteristic fibrillary tremor. In electromyographic observations (with Dr. S. Nevin) of the wasting muscles of patients suffering from muscular dystrophies including dystrophia myotonica, we have not observed true fibrillation.

(4) The Fasciculation of Muscle in Motor Neurone Disease.

Involuntary twitching of muscles has long been recognized as a feature of the course of amyotrophic lateral sclerosis, and its subvarieties, bulbar palsy and progressive muscular atrophy.

"The muscles whose nutrition is threatened, or actually damaged, are often jerked by little fibrillary or partial contractions. When this takes place the skin is seen to be raised and depressed as if by the tightening and loosening of delicate cords acting in the direction of the muscles. These contractions are of short duration, but they succeed each other with tolerable rapidity (at intervals of from one to four seconds) and occur in many points of the surface of the muscle. At other times the muscles are agitated with little worm-like movements. In some patients these contractions are almost continuous and occupy a whole limb or a great part of the surface of the body, while in others great attention is necessary to prove their existence, owing to their rarity and weakness, and often they need to be provoked by voluntary or electric stimulation, or by compressing or pinching the muscles. After such stimulation the reflex fibrillary contractions are stronger and more numerous. Partial or fascicular spasmodic contractions sometimes cause little movements of the limbs, especially of the fingers or thumb. Like the foregoing they are short and intermittent, but more rare." (From Duchenne, "L'Electrisation Localisée," third edition, p. 486, from Selections from the Works of Duchenne, Poore, 1883, London.)

In the brief periods of arrest characteristic of the disease, such twitching may disappear for weeks or months at a time. Where it occurs in flat muscles such as pectoralis major it can be readily seen that each twitch involves a bundle of muscle fibre 1 to 3 mm. or more wide, and is a sharp single contraction of that bundle, producing a momentary tightening of its whole length. When the twitching is not too intense it can also be observed that a particular bundle twitches steadily at a particular rate, which varies from one to another with long intervals of five seconds to two minutes. Where the twiching is intense the whole muscle is in continual coarse agitation and the twitching of it in any one place may appear to affect a large muscular bundle in different ways. Each particular shape of twitch is, however, repeated in exact manner after an interval.

In muscles which are extremely wasted, and covered only by a very thin layer of skin and subcutaneous tissue, such as the tongue or the first dorsal interoseus muscle of the hand, this coarse twitching may be seen to be combined with and later replaced by a fine " true " fibrillation such as has been described above for denervated muscle.

Electromyographic records of muscle in this state of coarse twitching (figs. 5 and 6) show that each fascicular twitch is accompanied by a single large action current. In a long strip of record it can be seen that both the mechanical deformation of the muscle surface, and the accompanying shape of the action current, are individual for each twitch and that each particular combination is repeated again and again at long intervals, such as 4·9 and 6·8 seconds for that shown in figs. 5 and 6. Where the twitching is too complex to identify individual twitches by the naked eye, the electromyographic and mechanical records still show that any one shape of twitch is repeated at relatively long intervals (figs. 7 and 10).

The regularity in position, size and shape of action current of each involuntary twitch of the " fasciculation " of this disease points to its being a *single impulse contraction in a fixed group of muscle fibres.* The group is smaller than a muscular fasciculus, but much larger than one single muscle fibre. The only functional group of this nature in muscle is the motor unit. If this twitching were the result of the reception of a nerve impulse by the whole group of muscle fibres supplied by a motor nerve fibre, it would follow that the origin of the impulse must be related either to a pathological process in the nerve fibre itself, or in the parent anterior horn cell. From the pathology of this disease we can suspect the latter.

This phenomenon, commonly called " fibrillation," but more properly called *" fasciculation,"* may therefore represent the intermittent involuntary discharge of single nerve impulses by an abnormal motor neurone. These abnormal action currents are in fact comparable in size and shape to the individual discharge of single moderate sized motor units. By instructing the patient to contract the muscle slightly by involuntary effort, the characteristic rhythmical discharge of normal motor units can be made to appear in the electrogram, accompanying the contraction. A strong or moderately strong willed contraction is accompanied by a confusion of action currents, but by arranging that a very weak contraction is produced, a few simple action current rhythms can be obtained (fig. 11). Discharge provoked in this way is a rhythmical series of nerve impulses at a rate of five to twenty-five a second. The resulting muscular contraction is a partly fused series of twitches, but the action currents, being much more brief, appear as a regular series of identical shape.

It was of interest to observe if a motor unit which showed " fasciculation " could be excited to normal willed discharge. Normally the *same* motor units always begin the discharge in a very slight muscular contraction—apparently particular units are always the first to contract in the beginning of that particular willed movement. We searched for "fibrillating " units which could thus be possibly called into activity early in slight voluntary movement, and in due course found several examples (fig. 8). Here there was no doubt that the disordered motor neurone could also discharge a normal series of identical nerve impulses in response to willed effort. It is presumed that the other fasciculating units also did so but came so late into contraction that their discharge was swamped in the resulting intensity of electrical fluctuation. The units observed in this way were fasciculating at moderately long intervals of five to thirty seconds. Voluntary discharge of this type enhances the " fibrillation " so that in the few seconds following the movement fasciculation is more rapid in that particular unit. This appears to substantiate our conclusion that the site of the abnormality leading to the involuntary twitching is closely related to the excitable portion of the neurone, the cell membrane or the synapse. The disorder is not *directly* related to the process of excitation, for these units are neither more nor less readily excited by voluntary effort than is any random unit sampled by the electromyogram. Their discharge was regular and not subject to abnormal lapses or ease of fatigue. We also observed that percussion and cooling enhanced fasciculation, apparently by also inducing a light voluntary discharge. On account of the naked-eye resemblance of early shivering to this twitching, we do not recommend these procedures for facilitating the observation of the disorder in the clinic, though the electromyographic record is distinctive in shivering (Denny-Brown, Gaylor and Uprus, 1935), being a grouped tetanic discharge.

In the course of a willed movement of moderate degree of any one muscle group at a joint, there occurs complete cessation of tonic and other action currents in the directly antagonistic muscle group. This is not necessarily true for contraction of synergists, but the discharge of the motor neurones is inhibited in the course of direct reciprocal innervation.

We have observed that the motor unit discharge of amyotrophic lateral sclerosis cannot be inhibited in this way by willed contraction of a direct antagonist as prime mover (fig. 9). We have therefore demonstrated that "central excitatory state" (Sherrington, 1929) can be set up, and the neurone thus caused to discharge naturally, and "central inhibitory state" is unaffected and does not interfere with fasciculation. These processes are related to the synapse. It is to be concluded that the disorder underlying fasciculation is situated in the cell body or its dendrites and not at or outside its surface, and is a precursor of atrophy of the neurone.

In wasting muscles the coarse fasciculation and fine fibrillation are concomitant, which is to be expected from the known true degeneration of the motor neurone which eventually occurs. Here the contrast between the size of the action currents of fibrillation and fasciculation can be seen in the same record (fig. 10). With needle electrodes only a small electrical field is sampled and the difference in size between muscle fibre action current and motor unit action current is therefore relative and not absolute.

(5) Fascicular Tremor Appearing with Contraction ("Contraction Fasciculation").

Coarse tremors of fasciculi in limb muscles are often observable in subjects of wasting diseases. Such tremor is liable to confusion with the spasmodic fasciculation of amyotrophic lateral sclerosis described above, especially since it may occur in combination with it in that disease, or alone in other affections, or with true fibrillation following poliomyelitis or polyneuritis. It is quite independent of either "true fasciculation" or "true fibrillation" in that it disappears completely with complete relaxation of the muscle.

In characteristic form it is seen as a coarse rhythmical tremor of a fasciculus at a rate of from 5 to 20 a second. The contraction is strong enough sometimes to cause wavering of an extended finger. With stronger contraction other fasciculi show similar tremors, but with moderate to maximal contraction the twitching grows more rapid and may be swamped by the contraction of other fibres in the muscle. In muscles such as pectoralis it can be observed that the contraction involves only part of a fasciculus.

In myographic records the twitching is a regular discharge exactly comparable to that of a motor neurone, though the resulting twitches of the muscle are poorly fused even at higher rates of discharge (figs. 12*b*, 12*c*). The individual mechanical twitches are much larger than those of the usual motor units to come early into action in a willed movement, and their discharge is not so rapid. The onset is always at a certain stage in a particular movement in the muscle concerned, sometimes with only slight postural contraction (fig. 12*a*). The phenomenon is encountered in our experience only where the muscle is notably wasted, but would appear to be the normal discharge of a very large motor unit.

The tremulous motor unit is not necessarily the first to discharge in contraction and when different muscles are observed the tremor is seen to enter the contraction at different stages. As has been stated above, a particular voluntary movement appears to begin always with discharge of the same motor unit. More intense contraction is secured by the addition of more and more units added in a particular sequence (fig. 11). This "recruitment" of motor units into willed contraction is identical with that occurring in certain reflexes (Liddell and Sherrington, 1923, Sherrington, 1929). The early motor units in normal gradual voluntary contraction are always in our experience small ones (fig. 11). The larger and more powerful motor units, each controlling many more muscle fibres, enter contraction late. In a muscle wasted by loss of many motor neurones graduation of contraction becomes uneven because large motor units become active without sufficient previous recruitment of small units to smooth their contraction. That they are contracting in the same manner with the rest of the muscle in a normal individual is indicated by the size of the action currents in intense contraction. Their frequency corresponds with that of the muscle sound (15 to 35 a second (Wollaston, 1810)) and appears to us its probable explanation.

We believe that the isolation of large motor units by relatively preponderating atrophy of small ones is an explanation which best serves the facts of "contraction fasciculation."

(6) COARSE LOCAL TETANIC FASCICULATION ("FALSE FIBRILLATION").

Clinicians recognize types of benign "fasciculation" or "fibrillation," which occur in muscles not subject to a wasting disease. Of these a twitching of the orbicularis oculi of the lower lid with fatigue or debility is one type within general experience. Occasional very localized twitching in a calf muscle is also common, and a more generalized form affecting the calf muscles and the small muscles of the feet and hands is described as "myokymia" after Schultze (1895) and Kny (1888). In the latter condition irregular contractions of fasciculi of muscles gives a slow undulation of the surface.

This type of contraction has a longer duration than that of the forms of fibrillation described above. For some one to three seconds the contraction pursues either rapidly interrupted course as is common in orbicularis oculi, or a deliberate sustained spasm. The contraction appears in the same place at irregular intervals, and is often large enough to make the subject conscious of its occurrence, and he cannot suppress it. It is not related to willed movement.

The *sensation* of twitching appears to result from the size of the structure involved, for other fibrillation is sensible according to its size, and in the type with which we are concerned here the structure involved is of the size of a whole fasciculus.

Records of such twitching confirm the impressions gained from visual observation. Both in the calf (fig. 13) and in orbicularis oculi (fig. 15) the twitch is in fact a partly fused muscular tetanus with repetitive nervous discharge which is irregular in time interval, and often in shape as well. The irregularity in shape of successive action currents points to a focus of irritation which is not nervous, but affects unevenly a bundle of nerve fibres to the fasciculus.

In a patient suffering from generalized myokymia, associated with cramps of the legs ("paramyotonia") we obtained records of both phenomena (fig. 14). In myokymia a fasciculus is suddenly involved in intense high frequency discharge lasting one-twentieth to one-tenth of a second (fig. 14*a*). The resulting contraction is a slow wave. This type of contraction occurs in different fasciculi independently and intermittently. A cramp takes the form of rhythmical high frequency discharge of this kind (fig. 14*b*). We observed the transition of the action currents of willed movement into periodic intense cramp action currents (fig. 14*c*). Occasionally the intense discharge will last a second or more without intermission, and then cease suddenly (fig. 14*d*) or become transformed into the intermittent type. The contraction is fascicular, and in our view is but an intense form of the fasciculation of fatigue (fig. 13).

While further examination of the focus is beyond the means at our disposal, we regard this phenomenon of "false fibrillation" and "myokymia" as one probably related to vascular cramp, or other change in the vessels which supply the fasciculus. Cramps in the same muscles commonly affect the subjects of myokymia. It has not in our experience been relieved by calcium, though improvement in the general health of the subject usually leads to its disappearance.

It is noteworthy in this connection that on the one hand Langley (1915-16*b*) noted that fascicular contraction occurred in frog muscle at a moderate stage of fatigue, and that on the other Kny and Schultze both noted in generalized myokymia that their patients suffered from greatly enhanced sweating. Excessive perspiration was also a disorder obvious in the two patients suffering from generalized myokymia observed by us. These observations indicate that fatigue may derange the excitability of the motor nerve in or near the muscle, and that disturbance of sodium chloride balance may in particular cause such derangement, in other forms than cramp. It may be stressed therefore that the incomplete relief of the condition by exhibition of sodium chloride indicates that the neurosis or exhaustion state underlying fatigue or hyperidrosis requires also to be treated in patients subject to this disorder.

(7) INVOLUNTARY MULTIFASCICULAR CONTRACTION IN AFFECTIONS OF 7TH NERVE.

The muscles supplied by the 7th cranial nerve are peculiar in that in stages of partial *regeneration* of the nerve a curious type of involuntary contraction and spasm appears (" post-paralytic contracture "). This is not " true fibrillation " for intermittent very small action currents in the electromyogram of the *completely* paralysed muscle indicate that " true fibrillation " is present, though not observable by inspection of the face by the clinician. Post-paralytic contracture is commonly observed following Bell's palsy and was described by Duchenne (1883). Babinski (1905) and Lamy (1905) observed the association of the spasm with inco-ordinate movements of the face, such as contraction of the frontalis when attempting to close the eye, and considered it to result from regeneration of the nerve fibres into abnormal channels. The exact manner of production of the spasm remains unexplained. It can be observed as intermittent flickering contractions, one contraction often affecting wide areas of the facial muscle, and each contraction varying from some half to five seconds in duration. By the overlapping of successive contractions moderately steady " contracture " is set up. When the phenomenon is slight in degree it may be seen only as momentary dimpling of the chin. It is not infrequently observed as a sign of affection of the 7th nerve by tumours in the lateral recess, and we have seen it occur as the first sign of a pontine attack of disseminated sclerosis, as is also described by Oppenheim (1911) and others. " Post-paralytic contracture " is quite distinct from psychogenic facial spasm, which is a stereotyped movement related to the tics.

Electromyographic records of " post-paralytic facial contracture " reveal successions of very rapid action currents of uniform size and shape (fig. 16). The size and regularity of each outburst is exactly comparable with motor neurone discharge, though the rate of discharge is greater than that of motor neurones in limb muscle. The outbursts occur at irregular intervals of one to thirty seconds or more. They are of increased frequency following any voluntary contraction of the muscle, and appear to affect the same nerve fibres as are innervated voluntarily, for an attempted movement causes these units to discharge also. These bouts of rapid discharge are periodic, as if a focus in the nerve fibre, or the motor neurone in the facial nucleus were intensely excited at intervals. We have not found any criterion to give a clue to the site of origin of the discharge. The electromyogram of this post-paralytic contracture closely resembles that of stretch responses in sodium contracture in muscle (Adrian and Gelfan, 1933) though in the face the discharge is nervous. Possibly the facial muscle is particularly sensitive to stretch in this way at a particular stage in regeneration. The electromyogram nevertheless indicates its fundamental difference from true fibrillation and true fasciculation, and the other forms described above. The electromyogram of tic-like facial spasm on the other hand is that if any voluntary movement in the face.

Bender (1938) in an interesting paper shows that the paralysed denervated facial muscles of the monkey enter a spasm when the animal is frightened. It is concluded that the phenomenon is acetylcholine contracture due to release of that substance into circulation by fright. Such contracture affects all the facial muscles at once, and disappears when regeneration occurs. In this manner it differs entirely from " post-paralytic contracture," which appears only with regeneration and affects isolated fasciculi. We have not observed this fright phenomenon in man.

(8) On Some Abnormal Contractions Elicited by Mechanical Stimulation of Voluntary Muscle, and their Relation to Fibrillation.

Schiff (1858) described the contraction elicited in striped muscle by direct percussion (" idiomuscular contraction ") and the persistence of the phenomenon in the animal recently dead. A localized knot of contraction immediately forms at the site of percussion, and series of small waves of contraction leave the knot on either side and travel to the ends of the muscle fibres, sometimes being reflected back again. Schiff and others have argued that these localized and slowly transmitted forms of contraction were related to the sarcoplasm and not to the sarcostyles (Joteyko, 1909). Langley and Hashimoto (1918-19) observed slow waves passing in both directions from a focus in a degenerating muscle fibre, but the phenomenon is rare as a spontaneous event in atrophic muscle. Its appearance immediately after death appears to be related to deficient oxygeneration for it can be produced readily by sodium sulphocyanide (Langley, 1915-16c) though other sodium salts delay its appearance in excised muscle (Milrad, 1885-86). Curschmann (1905), Klippel (1903) and others have noted the phenomenon of idiomuscular contraction in man and its intensification, with the appearance of the slowly transmitted waves, in patients suffering from various debilitating diseases such as phthisis, alcoholism, acute rheumatism. In these it can be observed especially well on percussion of the pectoral muscles, and was at one time considered of importance in the diagnosis of phthisis, though direct relationship was later disproved (Klippel, 1903). The localized contraction was called by clinicians "myœdema" (myoïdème). Curschmann (1905) concludes that its occurrence is but one aspect of a generally raised muscular excitability which may occasionally affect the nerves also.

We have observed the fully developed phenomenon in two patients with wasting of the muscles of the shoulders as part of a general cachexia from neoplasm, but with no other sign of nervous disease. We submitted one to electromyographic examination of the anomaly for comparison with true fibrillation and fasciculation.

In the normal person percussion of muscle induces a small local knot of contraction with tightening of the remainder of the fasciculus, and both subside in from one to five seconds according to the intensity of the stimulus. A sudden plucking pinch, sufficiently strong to be painful, of the belly of biceps brachii elicits it well. The electromyogram shows a large number of irregular fine action currents, indicating that local diffuse excitation has occurred, varying in degree according to the local mechanical damage.

When the "idiomuscular contraction" is present the local contraction appears as above, but the local contraction ("myœdema") subsides completely only after some ten seconds or more. It is accompanied by a few usual rapid action currents (fig. 17*a*, at *x*), and with brief general tightening of the fasciculus. The small transmitted wave leaves the knot of local contraction immediately, and we have recorded it as it passes a distant point on the same fasciculus, all of which it appears to involve. It travels at a rate calculated to be 2·08 cm. a second and last 0·7 sec. at one point. It has no action current (fig. 17*a*), though there is possibly a small negative variation. If action currents of willed contraction are present they are not abolished by the slow wave (fig. 17*b*).

Gelfan and Bishop (1932, 1933) and Gelfan (1933-34) have shown conclusively that it is possible to excite slowly propagated waves in striped muscle of the frog by stimulating the *contents* of the muscle fibre, either at its cut end, or by a localized mechanical stimulus. Such a slowly propagated contractile process was found not to be accompanied by an action current. These authors have proposed the reasonable hypothesis that the contents of the muscle fibre (sarcoplasm and sarcostyles inclusive) possess a separate irritability and rate of conduction. On this hypothesis the normal mechanism of conduction of the excitatory process very rapidly over the whole muscle fibre and rapidly stimulating the whole of it, is the "action potential mechanism." This appears to be a wave of depolarization passing over the sarcolemma, or outer muscle membrane, accompanied by an action potential. Thus normal contraction of a single fibre is rapid and possesses initial electrical variation.

On this view, which appears well founded, the phenomenon of idiomuscular contraction becomes the response of the whole muscle fibre to intense mechanical stimulation, and is made up of a momentary stimulation of normal twitch contraction, plus an intense and more lasting stimulation of the muscle fibre contents at the point of injury. This latter focus is the starting point of slow waves of contraction in the contents of the fibre. Under certain circumstances, among which the prominence of acute infections, gastric carcinoma, gastritis, and tuberculosis strongly suggest a factor of disturbed potassium:sodium ratio, the excitability of both sarcolemma and muscle fibre contents appear to be raised. We might therefore recognize in the phenomenon of idiomuscular contraction a disturbance of the excitability of the muscle fibre, predominantly of its contractile contents. In contradistinction, true fibrillation is a greater sensitization of the "action potential mechanism" (? sarcolemma).

Bremer (1932) has shown that the various varieties of physiological and pharmacological contracture in muscle can be related to two types of excitability normally present in muscle and our view of the phenomena of fibrillation and idiomuscular contraction would fall into line with this point of view, though we have not attempted to determine the excitabilities concerned.

In the earlier sections of this paper we have indicated that the clinical observation of fascicular twitching on the one hand and true fibrillary twitching on the other may be interpreted as due to enhanced irritability of the motor neurone, or the muscle fibre respectively. The occasional occurrence of fasciculation in the course of an acute toxic infection such as the onset of pneumonia, in association with enhanced idiomuscular contraction, would indicate that in such states the irritability of all the various parts of the motor unit may be disturbed. Such is also more commonly and consistently observed in the course of tetany, where fasciculation may be observed to lead up to enhanced reflex excitability of the motor neurone (West, 1935), and where enhanced idiomuscular contraction has been described (Curschmann, 1905).

CONCLUSIONS.•

(1) Close inspection of spontaneous twitching of muscle fibres reveals characteristics which enable the situation of the disturbance of excitability to be deduced. The single discharges of disordered anterior horn cells are thus distinguishable from the more coarse and longer twitches arising from affections of the intramuscular nerves, and both are distinct from the fine fibrillation of denervated muscle. Combinations of the various types may occur.

(2) Hyperexcitability of motoneurones in diseases such as progressive muscular atrophy or amyotrophic lateral sclerosis results in regularly periodic discharges of single impulses by the motor neurone. The focus of irritation is not at the synapse, but within the neurone. The resulting fasciculation at rest should be distinguished from rapid fasciculation during contraction (" contraction fasciculation ").

(3) Denervated muscle fibres contract periodically, and the confused medley of small twitches constitutes true fibrillation. The movement is so slight that it can seldom be seen in the clinic. The twitching appears to be due to heightened excitability of the sarcolemma, or rapidly conducting portion of the muscle fibre, to traces of free acetylcholine in the tissues.

(4) Re-innervated muscle is free from such involuntary excitation, except for the curious " contracture " of facial muscle, which consists of periodic intense repetitive discharge which suggests a central mechanism.

(5) In circumstances of fatigue or excessive loss of sodium chloride involuntary muscular contractions appear. Those due to fatigue are small bursts of contraction in a fasciculus, and are of a type such as would be caused by irregular discharge spreading to and through all the nerve bundles in the fasciculus. Those of myokymia, associated with hyperidrosis are of similar nature but of more widespread distribution, and more intense discharge. Both are clearly related to muscular cramp. The prolonged discharge, compared with the single twitch of fibrillation and the fasciculation of neurone discharge, gives the resulting fascicular movement a slower, undulating appearance.

(6) The excitability of the cytoplasm of muscle fibres may be disproportionately raised in association with cachectic states. Abnormalities of

the mechanical excitability of the muscle fibre then appear. Investigation of the sodium : potassium ratio in this connection would appear desirable.

We wish to acknowledge with gratitude the use of electromyographic apparatus provided by the Medical Research Council, and the permission given by various members of the Medical Staff of the National Hospital, Queen Square, to interest patients under their care in submitting themselves to this investigation.

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PLATE XVI.

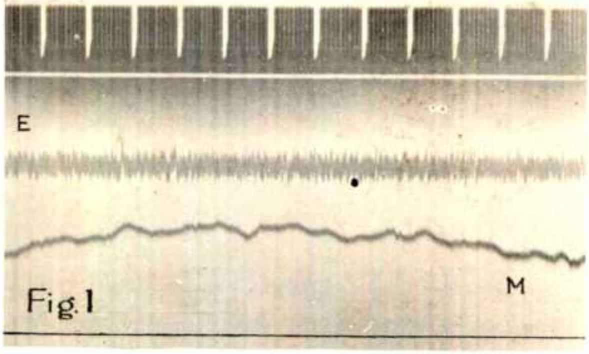

Fig. 1

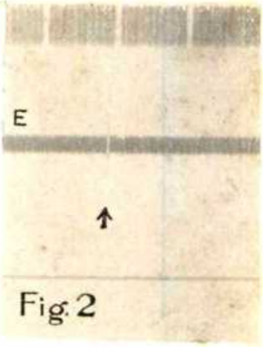

Fig. 2

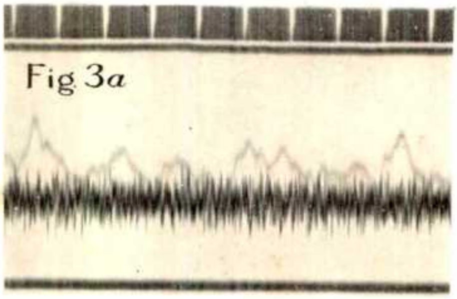

Fig. 3*a*

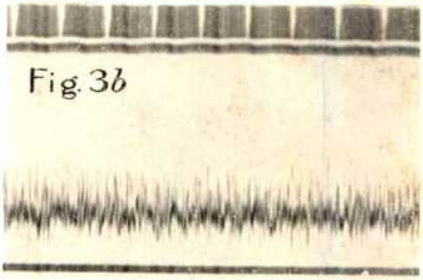

Fig. 3*b*

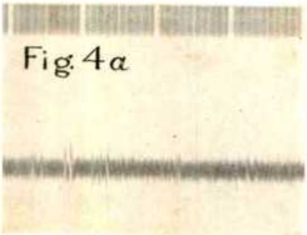

Fig. 4*a*

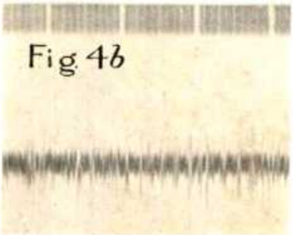

Fig. 4*b*

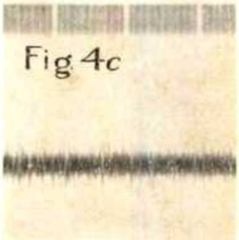

Fig. 4*c*

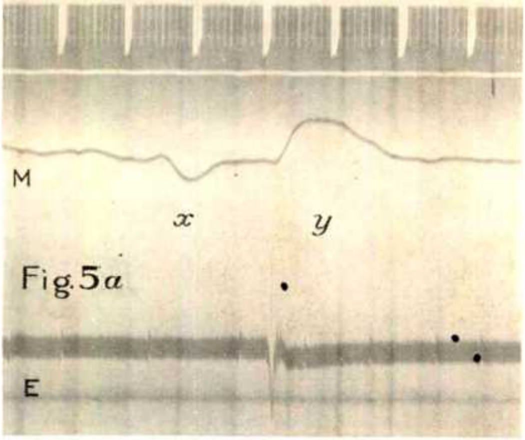

Fig. 5*a*

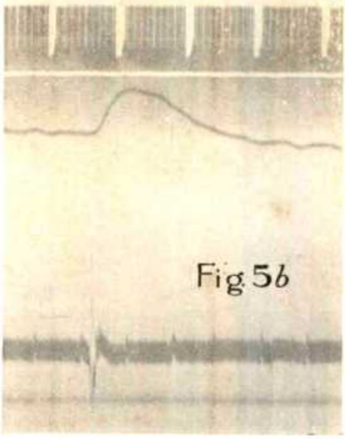

Fig. 5*b*

To illustrate article by D. Denny-Brown and J. B. Pennybacker.

PLATE XVII.

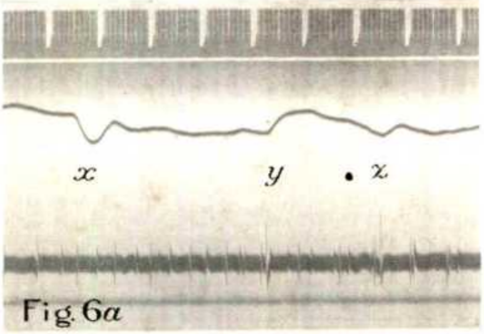

Fig. 6*a*

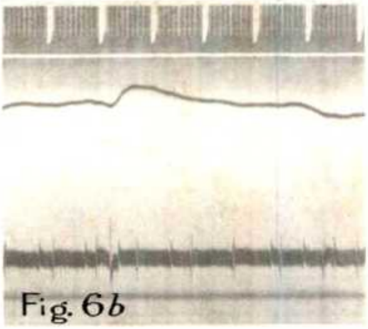

Fig. 6*b*

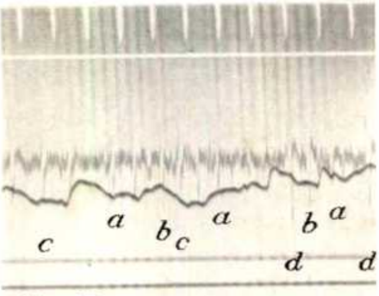

Fig. 7

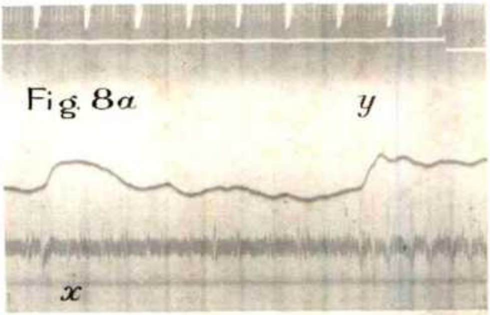

Fig. 8*a*

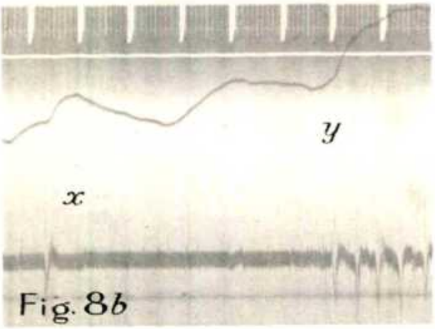

Fig. 8*b*

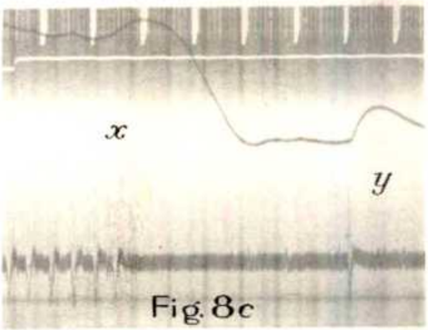

Fig. 8*c*

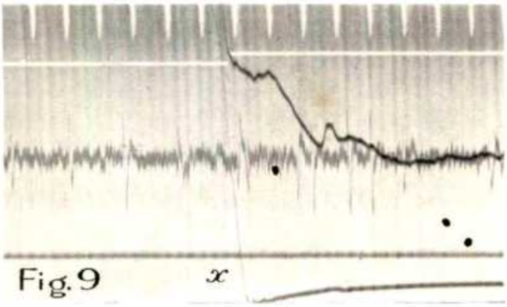

Fig. 9

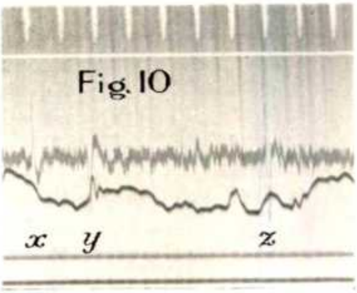

Fig. 10

To illustrate article by D. Denny-Brown and J. B. Pennybacker.

PLATE XVIII.

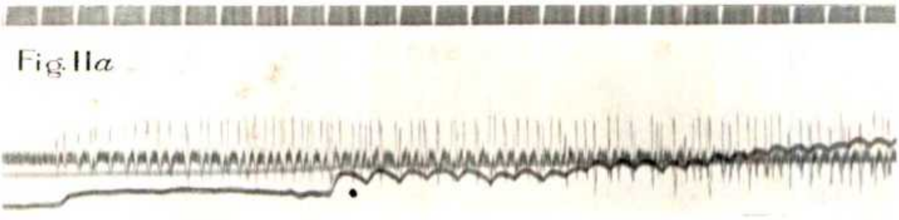
Fig. 11*a*

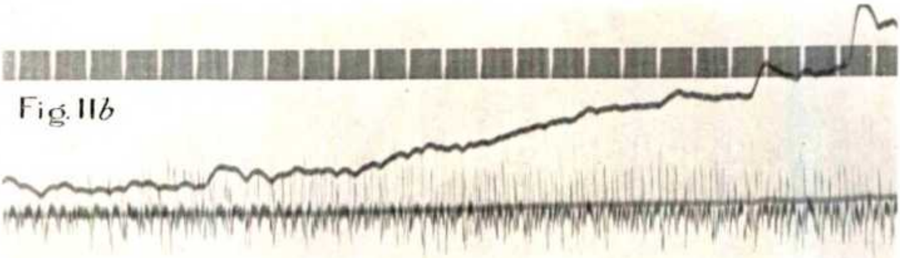
Fig. 11*b*

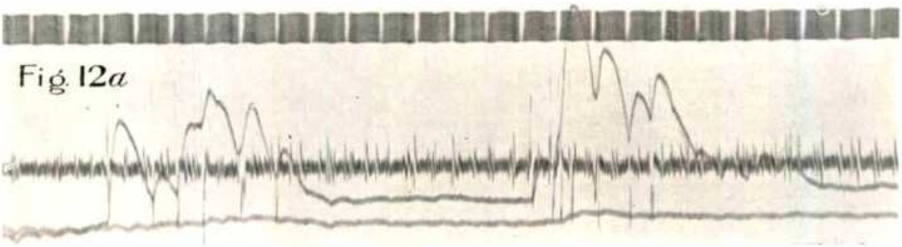
Fig. 12*a*

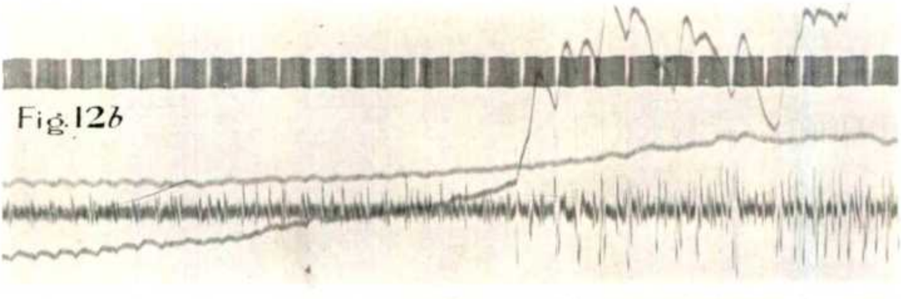
Fig. 12*b*

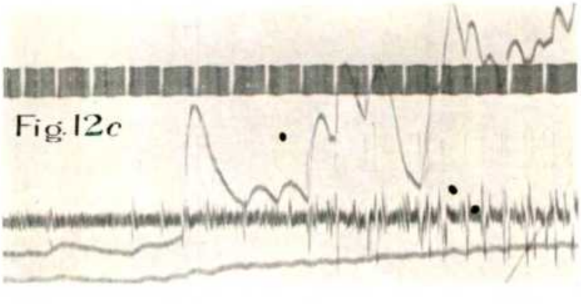
Fig. 12*c*

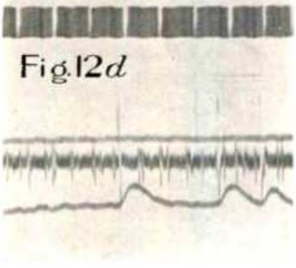
Fig. 12*d*

To illustrate article by D. Denny-Brown and J. B. Pennybacker.

PLATE XIX.

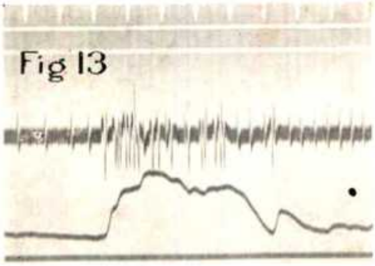
Fig 13

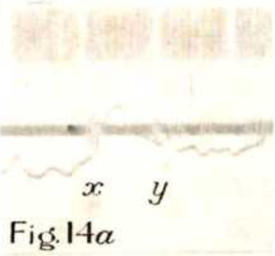

Fig. 14*a*

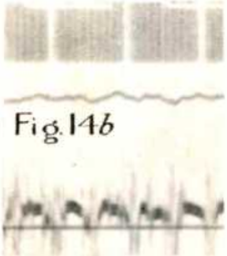
Fig. 14*b*

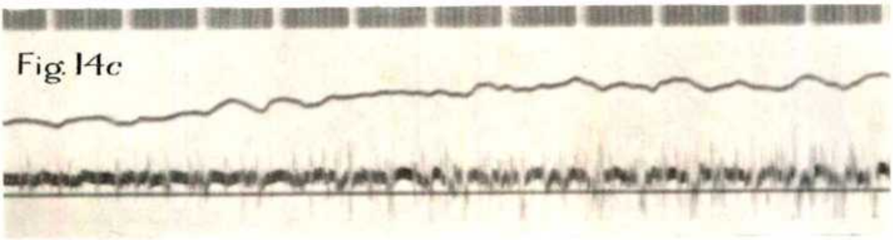
Fig. 14*c*

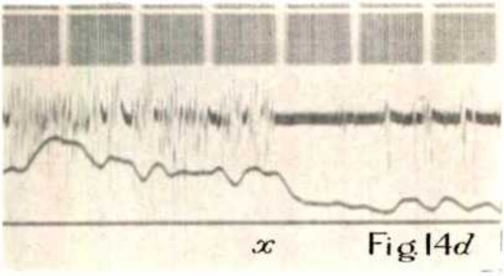

Fig. 14*d*

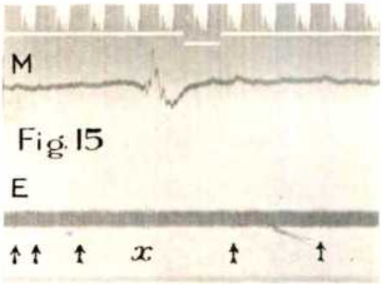

Fig. 15

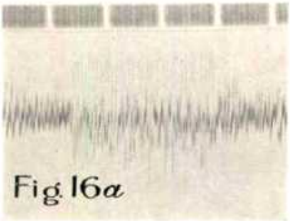
Fig. 16*a*

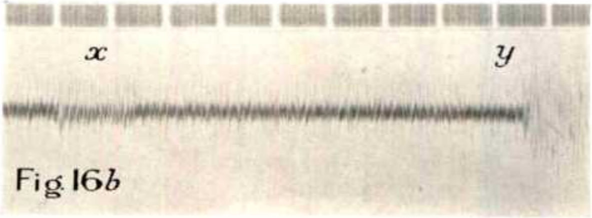

Fig. 16*b*

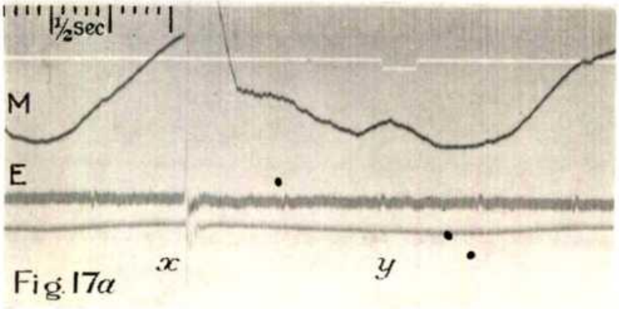

Fig. 17*a*

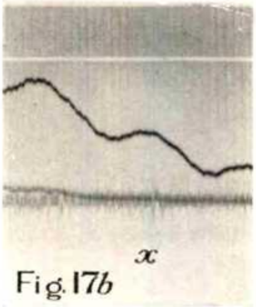

Fig. 17*b*

To illustrate article by D. Denny-Brown and J. B. Pennybacker.

DESCRIPTION OF PLATES.

All tracings read from left to right. Time marked by vertical lines at top of each record at 1/5 sec. intervals (except fig. 17).

PLATE XVI.

FIG. 1.—Mechanical (M) and electrical (E) tracing from the mylo-hyoid muscle of a patient suffering from wasting of the muscles of the tongue due to syringomyelia. The fibrillation was visible just under the mandible, where the muscle lies just under the skin. The vertical white strokes at the top of the record indicate intervals of 1/5 sec.

FIG. 2.—Electrical record from M. soleus, six days after section of sciatic nerve. Cat. Action current of fibrillation at arrow. This action current was repeated at intervals of 5·6 sec.

FIG. *3a.*—Mechanical and electrical record of fibrillation in M. soleus, cat, nine days after section of sciatic nerve.

FIG. *3b.*—Electrical record of intense fibrillation in M. gastrocnemius nine days after section of sciatic nerve.

FIG. 4.—In 4a is shown the action currents of soleus seven days after nerve section. Some four seconds later about 0·1 c.c. of 1 : 500,000 acetylcholine in saline is injected into the muscle at its origin. The reaction after about a second is shown in fig. 4*b*. Thirty seconds later the electromyogram is that shown as Fig. 4*c*. Cat. Time 1/5 sec. intervals.

FIG *5a.*—Left pectoral muscle of patient suffering from amyotrophic lateral sclerosis, with coarse fibrillation. Mechanical (M) and electrical record (E) of a fasciculus of the muscle. At *x* there occurs a twitch in the underlying intercostal muscle. At *y* a twitch occurs in the fasciculus with accompanying action current.

FIG. *5b.*—As fig. *5a,* showing an identical twitch and action current 4·9 sec. later. Time 1/5 sec. intervals between large white strokes.

PLATE XVII.

FIG. *6a.*—Pectoralis muscle of patient suffering from amyotrophic lateral sclerosis. Slight postural contraction is present, with rhythmical discharge of three small motor units. At *x, y,* and *z,* there occur three fascicular twitches. That at *x* is in the underlying intercostal muscle and is without action current. Those at *y* and *z* occur in the fasciculus from which the record is taken, and are different in both the mechanical and electrical record.

FIG. *6b.*—A continuation of the record of fig. 6*a* showing repetition of the twitch *y* of record 6*a* after an interval of 6·8 sec. Time intervals of 1/5 sec.

FIG. 7.—M. triceps of patient suffering from amyotrophic lateral sclerosis in advanced stage. Showing rapid coarse fasciculation and fine fibrillation. The muscle was very weak and atrophic. In the confused electromyogram various shapes of action current marked *a, b, c, d,* are being repeated at intervals varying from 0·5 sec. to 10·0 sec. and longer.

FIG. 8.—M. pectoralis major. Amyotrophic lateral sclerosis. In fig. 8*a* a spontaneous fascicular twitch occurs at *x*. At *y* the patient commences a slight willed movement, with resulting repetitive discharge and contraction of the same motor unit. In fig. 8*b* a similar twitching unit in another part of the muscle is seen at *x*, and its discharge in response to willed effort at *y*. The action currents are identical. In fig. 8*c* the same voluntary discharge as in fig. 8*b* is seen terminating 1·8 sec. later. Enhanced fibrillation begins at *y*, and for three irregular beats occurred at intervals of about 0·6 sec. on the continuation of the tracing after *y*.

FIG. 9.—M. triceps. Amyotrophic lateral sclerosis. Severe fasciculation. The patient was strongly innervating the flexors of the elbow before the record begins. He ceases at *x* and relaxes. Coarse fasciculation and fibrillation occur irregularly during the effort, which abolished all central discharge of other kind in the muscle. The fasciculation is a little more frequent in the first second following reciprocal inhibition and then settles down to the usual irregular rhythm.

Fig. 10.—M. triceps. As fig. 7. Showing various types of twitch of one large fasciculus in an advanced stage of the disease. That marked *x* had occurred 4·4 sec. earlier and was repeated 5·4 sec. later. That marked y had occurred 4·8 sec. earlier, and recurred 5·4 sec. later. That marked *z* had occurred 8·2 sec. earlier and recurred 2·3 sec. later.

PLATE XVIII.

Fig. 11.—A normal voluntary contraction of M. biceps brachii. In the electromyogram the rhythmical discharge of motor units is seen to become more intense by the addition of further separate rhythms, each in a slightly larger size of action current. After a lapse of 2·2 sec. the record of fig. 11*a* is continued as fig. 11*b*, showing further increase of the movement by accrescence of further and larger electrical and mechanical units. Time 1/5 sec.

Fig. 12.—M. biceps. From a patient with progressive muscular atrophy, showing at this time only fasciculation during muscular contraction. The muscles were wasted. Fig. 12*a* shows occasional periodic twitching during a slight posture. Fig. 12*b* shows the twitching in another unit coming late into a willed movement. Fig. 12*c* shows the twitching occurring early in another willed movement. Fig. 12d shows occasional isolated twitches with slight movement such as holding the limb forward.

PLATE XIX.

Fig. 13.—M. biceps brachii. Patient with general asthenia. A coarse fascicular wave of contraction lasting a second is recorded on a background of slight postural discharge (one unit recording). Time 1/5 sec.

Fig. 14.—M. gastrocnemius. Patient with myokymia and cramps in both lower limbs. In fig. 14*a* a wave of myokymia occurs at *x*, accompanied by very rapid discharge in the electromyogram lasting 0·4 sec. Some slight normal discharge occurs at *y*. In fig. 14*b* is shown the electromyogram of an intense cramp, with periodic high frequency discharge. The patient was endeavouring to relax the muscle without success. In fig. 14*c* a voluntary movement develops into a cramp, with change of a normal action current rhythm into high frequency discharge. In fig. 14*d* a cramp is seen to end suddenly at *x*.

Fig. 15.—From a patient suffering from debility, with involuntary twitching of the lower eyelid. A small series of jerks in the mechanical record (M) is accompanied by a small repetitive action current, one to three diphasic waves in very rapid succession. Each group is indicated by an arrow. At *x* the patient blinked.

Fig. 16.—Facial palsy with partial recovery. Fig. 16*a* shows one of the frequent action current discharges which accompanies the spasm. The muscle is also fibrillating. Fig. 16*b* shows a motor unit discharging in slight voluntary expression involved in a bout of spasm at *x*, and entering intense discharge with other units at *y* in response to the command, " show your teeth."

Fig. 17.—Patient with cachexia from carcinoma. M. pectoralis major. Myogram from strenal end of a fasciculus, and electrical leads from this point also. A slow regular fluctuation in the myogram (M) is due to respiration. At *x* at the height of an inspiration the fasciculus is percussed heavily at a point 3·75 cm. away from the point recorded. The whole faciculus immediately tightens for 0·4 sec. after one large action current. 1·8 sec. later a wave, which had been observed to leave the point percussed, reached the electrode, an observer depressed a signal key to show he had seen it arrive. The hump in the myogram at *y* records its passing. There are no fresh action currents at this time. The electrocardiogram appears faintly in the record. The time marker lines are faint, and a period of 1·5 sec. has been stressed in tenths at the beginning of the tracing. In fig. 17*b* a similar wave is recorded during slight voluntary contraction. The action currents of voluntary contraction are unaltered by the wave.

NOTICES OF RECENT PUBLICATIONS.

The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects. By W. E. LE GROS CLARK, J. BEATTIE, G. RIDDOCH and N. M. DOTT. Edinburgh: Oliver and Boyd. 1938. Pp. 211, figs. 104. Price 12s. 6d.

The hypothalamus has for the time captured the interest that in recent years was enjoyed by the corpus striatum, the peripheral autonomic system and—still more ephemerally—by the so-called "premotor cortex." The present symposium of lectures delivered under the auspices of the Ramsay Henderson Trust by the authors named above will provide a useful summary of modern knowledge and current views. The anatomical section contains a clear, comprehensive and well-illustrated account of the comparative and human anatomy of the hypothalamus and hypophysis, while Professor Beattie contributes a précis of the experimental physiology of these structures. Dr. Riddoch summarizes the clinical manifestations of disease involving them, while Mr. Dott, with some unnecessary repetition of this matter, discusses the surgical treatment that may be possible. The last-named section will be of greatest interest to surgeons, and its superabundant illustrations will encourage them by that winning air of simplicity they impart to the necessary procedures.

The Brain and its Development. By J. BARCROFT. Yale University Press, New Haven. 1938. Pp. 111. Price $2.

In these fascinating lectures Professor Barcroft traces the development of central nervous activity in the growing fœtus, relating this to the interaction between the internal and external media in which the fœtal brain finds itself. The chemical milieu that bathes the developing brain has a stability that reaches its highest refinement of regulation in man, a factor which the lecturer suggests as having in all probability played a part in the development of man's intellectual powers. The first indication of a disturbance of this stability is always an impairment of the highest qualities of the brain.

The ascending order in which the reflex mechanisms of the cord and the brain-stem are seen to take up their functions in the fœtus affords an interesting commentary on their activities in post-natal life, as these have been revealed by the experimental physiologist, while the successive disappearance of these functions from above downwards on successive descending transections of the neuraxis completes that picture of evolution and dissolution of function of which Jackson wrote.

The Doctrine of Signatures. A Defence of Theory in Medicine. By SCOTT BUCHANAN, Professor of Philosophy in the University of Virginia. London: Kegan Paul. 1938. Pp. 205. Price 7s. 6d.

This philosophical essay will have for the medical reader a paradoxical air, since it urges a return to the principles of Aristotle and Galen, the men who loomed so authoritatively, and as many think deadeningly, over mediæval medicine and science. But it is the ancient distinction between form and matter, and the rational and teleological aspects of Galen's thought that are here put forward as the proper basis for speculative advance in medicine. Since psychiatry is the branch of medicine in which philosophical, and even metaphysical, issues are nearest the surface, there is much to confirm Professor Buchanan's sorrow that the popular philosophies which are so widely espoused by psychiatrists are not better understood as disguised and truncated Aristotelianisms: the sciences which grow precariously out of them, he says, fail at crucial points and frustrate their own rational developments. His brief references to homœostasis and "the pious talk about the unity and wholeness of the organism" are refreshing; confusion and loose generalization, while still widespread, are more easily spotted by such an outside observer, perhaps, than by doctors themselves. The author's plea for the revival of the liberal arts of the trivium and their application to medicine is lucidly and attractively expounded; it deserves the attention of those who are aware of the influence philosophical theories have had in the history of medicine and who are not blind to the crudities and culs-de-sac in some of the medical sciences to-day.

Les Arachnöidites Opto-chiasmatiques. Par J. Bollack, M. David and P. Pleech. Paris: Masson et Cie. 1937. Pp. 300, figs. 76. Price 70 Fr.

This is a really good monograph and deals with a subject the importance of which is becoming more widely realized. Arachnoiditis affecting the optic chiasma appears to be either more frequent or more commonly recognized in France than in England, for of the 129 case-records on which this work is based no less than sixty-six are from a single neuro-surgical department, viz. that of Dr. Clovis Vincent at the Hôpital de la Pitié. In every one of these cases the presence of chiasmal arachnoiditis has been verified at operation or post-mortem examination.

Having defined their subject and given a brief historical outline of the recognition of arachnoiditis, the writers demonstrate the normal anatomy of the region of the chiasma and then the abnormalities found in cases of arachnoiditis. The illustrations are numerous, lucid and convincing. Another excellent chapter is that on symptomatology. According to the authors' statistics the commonest syndrome produced is (bi-lateral) central scotoma, this occurring in 31 per cent. of cases. The next most frequent syndrome is simple constriction of the visual fields, and these two groups together make up 54 per cent. of cases. The classical bi-temporal constriction of the fields occurs in only 17 per cent. and other hemianopic syndromes in a further 13 per cent.

The differential diagnosis, forms of treatment, and results, are discussed in the later chapters, and there are analytical tables of all the previously published cases and of the cases personally studied by the writers.

It is evident that the authors are past-masters of their subject, have important matter to present and know well how to present it clearly.

Les Méningo-Neurobrucelloses. Par H. Roger and Y. Poursines. Paris: Masson et Cie. 1938. Pp. 248. Price 45 Fr.

In this valuable monograph the authors bring to notice the fact, hitherto scarcely appreciated by those interested in the Brucella infections, and virtually unknown to neurologists, that these infections are characteristically neurotropic and give rise to a wide range of clinical disorders of nervous function, and this not rarely, but commonly.

They open their account with a general statement of the ætiology and clinical features of Brucella infection, and follow this by a detailed description of the clinical pictures of central and peripheral nervous disorder due to invasion of the nervous system by the responsible organism. The reaction of the meninges, as indicated by examination of the cerebrospinal fluid, is described, but unfortunately there is no account of the morbid anatomy of the nervous system.

The clinical descriptions indicate that nervous involvement occurs late in the course of the infection, and that all parts of the nervous system, meninges, brain, spinal cord and peripheral nerves may be affected.

The studies recorded in this excellent monograph form a notable addition to clinical neurology, and one with which the neurologist should be familiar.

Textbook of Neuro-radiology. By C. P. G. WAKELEY and A. ORLEY. London: Baillière, Tindall and Cox. 1938. Pp. xiv and 336, figs. 229. Price 25s.

The increasingly valuable role of radiography and its various applications in neurological diagnosis make a textbook devoted to this subject a welcome addition to neurological literature. It is probable, however, that the chief value of the present work will be that of a technical guide to neurological radiography for the practising radiologist. The various methods and devices in use for the demonstration of the many pathological changes in the skull and its contents, and in the vertebral column, that are capable of being seen in a radiogram, are described in detail.

Brief clinical descriptions are given of most of these lesions, but these are of doubtful value because they are too short, and do not always emphasize—or even mention—the clinically salient features. Thus, meningioma of the ethmoidal groove is dismissed by the bald statement that its chief diagnostic feature is anosmia—a plainly inadequate summary.

The occurrence of such misspellings as "exopthalmus," "gliomasis" and "subternorial," indicate that greater care in proof reading would have been advantageous. The illustrations are good, but the different sections are unequally supplied in this respect and many of the reproductions of radiograms too small to show adequately the features they are intended to display.

Diabetes Insipidus. By C. FISHER, W. R. INGRAM and S. W. RANSON. Ann Arbor, Michigan: Edward Bros. Inc. 1938. Pp. 196. Price 5 dollars.

This volume embodies the details and results of a series of investigations on the structure and functions of the hypothalamico-hypophyseal system. A salient feature in the experimental method has been the production of lesions in the hypothalamic region by the Clarke-Horsley stereotaxic instrument. There is a detailed clinical study of diabetes insipidus in the cat, and an account of the normal anatomy of the hypothalamus and hypophysis in this animal. Finally, there is a long critical discussion of the relative merits of the hypothalamic and hypophyseal hypotheses concerning the origin of diabetes insipidus.

The authors conclude on the basis of their own observations that: the neural division of the hypophysis controls the flow of water through the kidney, and in respect of this function it fulfils the postulates of an endocrine gland, and on the following grounds: (1) Because its extirpation or atrophy secondary to interruption of the supra-optico-hypophyseal tracts leads to a deficiency symptom, namely, diabetes insipidus. (2) Because a potent antidiuretic principle can be extracted from it which, injected in minute amount into the blood-stream, produces a marked effect. (3) Because the neural division appears to elaborate this hormone. (4) Because the deficiency symptom can be alleviated by substitution therapy, i.e. the administration of extracts of the neural division containing this antidiuretic hormone.

This book is photolithographed from typescript, the object being to permit of the inexpensive production of scientific works that necessarily command a limited circulation.

Psychotherapy. By PAUL SCHILDER. London: Kegan Paul, Trench, Trübner and Co. 1938. Pp. 344. Price 15s.

The author's expressed purpose is to provide the student, the general physician and the psychiatrist with a knowledge of the technical procedure and the scientific principles upon which to base an approach to psychotherapy. It may be questioned, however, whether with no further knowledge than can be gleaned from so concise a summary of so vast and complex a subject, or without prior experience, the circle of readers named could hope to become successful psychotherapists. Possibly the technique of a physical or of a biological science can be usefully imparted in this simple way, but the thesis that psychotherapy is wholly based upon scientific principles and has no element of art in it is a mode of " wish-fulfilment " that not all will achieve so easily as the author appears to have done. That there is both an art and a science of medicine is an admission that no medical man finds it difficult to make, and psychotherapy will begin to approach the scientific more nearly when its exponents find it possible to make a similar admission. That he should find it impossible to do so indicates that for the psychotherapist, as for the rest of his professional brethren, the command " physician, heal thyself," is still a counsel of perfection.

The various questionnaires given for the benefit of the psychotherapist suggest strongly that the approach to the patient must take account of what the author calls his " ideologies," for they are manifestly not suited for general use, and if so used would bring many budding psychotherapeutic essays to an abrupt conclusion. There is to-day a vast amount of literature and discussion devoted to the study of the *homo sexualis* of Freud and the *homo economicus* of Marx, and the psychotherapist seems so deeply preoccupied with the former of these abstractions that he has overlooked the actual existence of *homo sapiens*. For this Cinderella of the psychologist's cosmos we see small hope of relief—should he ever need this particular form thereof—from a psychotherapy that takes such small account of so many and so important elements in his aspirations.

A Source Book of Gestalt Psychology. By W. D. ELLIS. London: Kegan Paul, Trench, Trübner and Co. 1938. Pp. 403. Price 21s.

The author has translated and reprinted summaries of thirty-four articles which have appeared in Germany during the fifteen years following 1915. Part I contains a statement of the general framework of Gestalt psychology, and Part II gives experimental and clinical details. There is a final section dealing with the various criticisms that have been made by opponents of this school of psychology.

The book is a valuable source of information for all who wish to keep abreast of modern thought in psychology.

DECEMBER, 1938

BRAIN.

PART 4, VOL. 61.

TUMOURS OF THE THALAMUS—A CLINICO-PATHOLOGICAL STUDY.

BY G. E. SMYTH AND KARL STERN.

(From the National Hospital, Queen Square.)

THE following study was undertaken with two objects in view. The first was to determine whether the development of tumours in the thalamus is fortuitous and without special characteristics, or whether amongst the great variety of tumours involving this structure a group could be identified having some characteristic features, such as a peculiar mode of development or of expansion. Examination of the material available at the National Hospital appears to indicate that there is a type of glioma which, arising in the thalamus, tends to expand along the wall of the 3rd ventricle, the walls of parts of the lateral ventricle and of the iter, and to invade adjoining regions of the brain in a lateral direction rather than ventrally towards the tuber.

The second problem was concerned with the degree to which the symptomatology of thalamic lesions, as determined from the study of vascular lesions by Edinger (1891), Dejerine and Roussy (1906), Holmes and Head (1911), was reproduced by new growths.

We have been impressed by the discrepancy to be noted between the symptomatology of thalamic tumours and the classical thalamic syndrome. Therefore a study of the clinical picture of thalamic tumours seemed desirable. Six cases were studied for this purpose, and the record is amplified by the consideration of cases reported in the literature.

MATERIAL AND METHOD.

The formalin fixed tissue was imbedded in celloidin and cut in serial sections. In view of the marked secondary mechanical and vascular damage produced by tumours it appeared superfluous to undertake a detailed study of single nuclei and fibre tracts, and, therefore, it seemed adequate to stain each 25th section. Blocks had already been removed from each case for routine examination, and these gaps had to be reconstructed in the light of the macroscopical post-mortem photographs. The serial sections were stained by Nissl's method. In addition van Gieson hæmatoxylin, Mallory's phosphotungstic acid hæmatoxylin, hæmatoxylin-eosin, Holzer's and Weigert-Pal's stains were applied to representative sections. Trial sections from various parts of the cortex were stained with Scharlach-R, Nissl's, and v. Braunmühl's stains in order to exclude general cerebral diseases.

TUMOURS INVADING THE THALAMUS FROM THE VENTRO-LATERAL PERIPHERY.

Case 1.—D. M., a man aged 50, was admitted to the National Hospital under Dr. Gordon Holmes on April 16, 1937.

The first symptom of his illness in August, 1936, was a persistent sensation of weakness of his right wrist. Within a few weeks there was a deterioration of fine movements of the fingers, and by December the right arm was weak and this was followed by slight weakness of the right leg. These disabilities slowly increased and two weeks before admission he became unable to shave himself. He did not admit to any sensation of numbness but suffered frequently from a dull aching pain in the right arm. For three weeks he had had severe vertical and occipital headaches which constantly awakened him at about 5 a.m. and lasted for the greater part of the day. Occasional brief diplopia on looking to the left had been present for one week and during this time there had been a persistent blurring of vision which, he insisted, was quite independent of diplopia. In other respects he felt well; appetite was good and, if anything, he was gaining weight. For about three weeks he had been sleeping unusually well and often had dozed during the day, a thing he had never done previously. The patient had been seen in private consultation by Dr. Gordon Holmes on March 24, 1937. At that time he complained of weakness and clumsiness of the right limbs and of numbness and aching of the right arm. Headache and visual disturbances had not then appeared. The significant findings recorded by Dr. Gordon Holmes were: Considerable weakness of the right lower face and deviation of the tongue to the right; marked loss of sensibility for prick, touch and temperature on the right half of the face with absence of the corneal reflex. There was no papillœdema, the visual fields were full and there was no abnormality of the extrinsic or intrinsic ocular muscles. The limbs on the right side were rather stiff and power was slightly reduced, proximal and distal segments being equally affected. There was considerable ataxia of the right limbs. The tendon-jerks were exaggerated on the right and the right plantar response was a doubtful extensor. On the right half of the body there was much sensory loss for touch, prick and temperature and great loss for posture, form and vibration. Dr. Gordon Holmes considered that the patient had a progressive lesion, probably neoplastic, deep in the left hemisphere and, from the amount of sensory disturbance, that it lay near the thalamus.

Examination.—April 16, 1937: The patient was a well-built florid man who co-operated well. Speech and intelligence were entirely normal. He was right handed.

Taste, smell, and hearing were normal. Vision was $\frac{6}{6}$ in each eye. On confrontation with a 5 mm. white disc there appeared to be a slight limitation of the right homonymous fields but this observation was not confirmed by subsequent perimetry. The fundi were normal. The external ocular movements were full. There was no nystagmus, ptosis or diplopia. The pupils were equal (5 mm. in diameter) and circular in outline. They were fixed to direct and consensual light but contracted promptly and fully on convergence. The jaw muscles were normal. There was a marked weakness of the right lower face in both voluntary and emotional movement. The tongue deviated to the right. There was hypoalgesia, hypoæsthesia and impaired temperature discrimination over the whole territory of the right trigeminus, and the right corneal reflex was less active than the left. The remaining cranial nerves were normal.

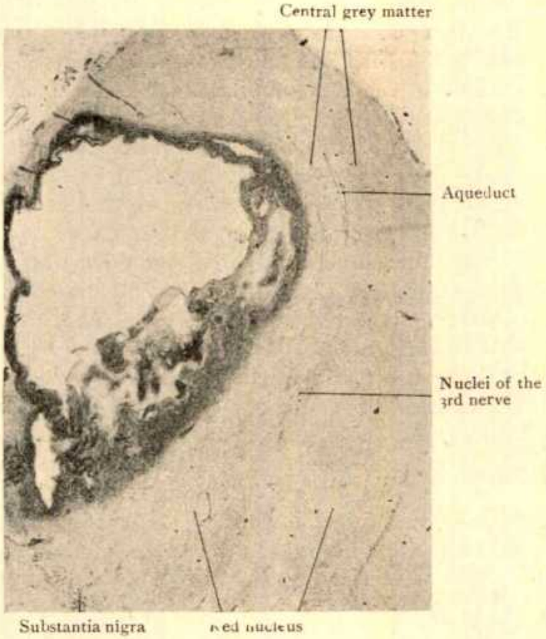

FIG. 1.—*Case 1.* Situation of the tumour in the rostral part of the mid-brain (Nissl. Approx. × 4.)

There was some hypertonus of the right arm and leg, and power was a trifle diminished. Tests for co-ordination revealed a gross ataxia of the right limbs. Alternating movements were carried out clumsily on the right.

On the right there were increased tendon-jerks, ankle clonus, diminished abdominal reflexes and an extensor plantar response.

There was marked impairment for touch, pain, pressure pain and temperature discrimination on the right half of the body. The area of sensory loss came to within one inch of the mid-line and was as deep on the trunk as on the periphery of the limbs. There was a gross loss of postural sensibility in the right arm and leg. The arm was the more severely affected and here the elbow and shoulder were as much affected as the wrist and fingers. It was impossible to find a threshold for compass points on the right hand and there was a total failure of primary recognition when common articles were placed in the right hand. Vibration was not perceived on the right arm, on the right leg it was diminished.

The cardiovascular system was normal. Blood-pressure 150/100. Examination of other systems showed no abnormality.

Cerebrospinal fluid.—Initial pressure 140 mm. of water. Cells less than 1 per c.mm. Total protein 0·160 mgm. per 100 c.c. Globulin positive. W.R. negative in blood and fluid.

Progress.—April 26, 1937: Strong pin-prick caused an exaggerated response on the right half of the body. The pain was less tolerable than on the unaffected side and it radiated widely. This perverted response persisted until death.

May 6: There was marked limitation of upward movement of the eyes and an attention hemianopia in the right upper homonymous quadrants.

May 25: The right hemiplegia was complete and the arm and leg were flaccid. The tendon-jerks were diminished although relatively more active on the right. Both plantars were extensor. He sank slowly but there were great fluctuations from day to day. He alternated between a light stupor and deep coma.

June 3: There was a definite right homonymous hemianopia. The right eye was turned inwards and a little downwards and there was weakness of conjugate movement to both sides. The limitation of upward movement was not quite complete and was greater on the right. There was inability to converge. The pupils were rather small (about 3 mm.), equal and entirely fixed. Throughout the illness the pulse and temperature were normal.

Post-mortem examination.—The body of a rather thin middle aged man. Right arm and leg rather more wasted than the left (½ inch difference at the middle of the upper arm). The brain alone was examined. There was a slight cerebellar pressure cone. On examining the mid-brain both anteriorly and posteriorly the left crus was seen to be diffusely swollen and less white than the right. There was a slight degree of ventricular distension. On section of the fixed brain a circumscribed tumour mass was encountered which was rather degenerated and showed large greenish-grey gelatinous areas. It occupied the larger part of the left tegmentum and the left thalamus. It extended caudally to the level of the nucleus albus and orally up to the anterior part of the lateral nucleus of the thalamus. In its lower part it occupied the whole parabigeminal area and a lateral zone of the red nucleus leaving only a small rim of the superior colliculus intact. In its upper part it occupied the lateral part of the thalamus and the adjacent part of the internal capsule and the lenticular nucleus (mainly globus pallidus). The anterior and medial nuclei of the thalamus were macroscopically intact.

Microscopical examination showed a large-celled glioma with a marked tendency to degeneration. Apart from large glia cells (many of which were multinucleated or in mitosis) there were numerous smaller cells of various types. In some places there was a perivascular arrangement but this was not constant, many vessels showing no attachment to neuroglial cells. All varieties of degenerative change were seen in the nuclei of both large and small cells but mitoses were more common in the large cells. The vessels showed chiefly thickening of the media but intimal proliferation was seen in some. Although the tumour in its single elements was rather polymorphous, the appearances were essentially the same at all levels which were examined. From the great number of large multinucleated cells and from the large protoplasmic astrocytes it resembled most closely the variation which Roussy and Oberling (1931) described as the giant cell astrocytoma.

Blocks from the material still available, were imbedded in celloidin and a series of 47 sections (20 μ) was stained with thionin.

On attempting to reconstruct the tumour stereoscopically it was found to consist of an elongated cylindrical mass with irregular processes. It extended from the genu of the left internal capsule, at the level of the broadest extension of the lenticular nucleus, downwards to the level of the inferior colliculus. The greater part of the lenticular nucleus, the genu, and the anterodorsal part of the internal capsule were destroyed. The ventral part of the lateral nucleus, almost the whole of the zona reticulata, the ventral nucleus and the larger lateral part of the pulvinar had disappeared. The lenticular fasciculus and the zona incerta were entirely destroyed and here the tumour occupied the dorsal capsule of the subthalamic nucleus (Luys), compressing this nucleus and invading a small dorsolateral part of it. A process of tumour tissue extended through Wernicke's field into the most proximal part of the optic tract at the point nearest to the lateral geniculate body. The medial and lateral geniculate bodies lay within the zone of glial and mesodermal reaction surrounding the tumour. At this level the tumour occupied the greater part of the anterior colliculus and the area adjacent to it, the parabigeminal area (Mingazzini), the areas of the medial lemniscus, the dorsal portion of the quinto-thalamic tract, and the outer (more cellular) zone of the central grey matter and compressed the aqueduct into crescentic form (fig. 1). The red nucleus was much compressed, and its dorsolateral part was invaded by tumour tissue. At this point a lateral process of the tumour extended through the dorsolateral cell group of the substantia nigra into the corresponding segment of the peduncle. The most caudal part of the growth invaded chiefly the parabigeminal area, the more caudal level of the medial lemniscus and the lateral capsule of the red nucleus, interrupting many of the fibres of the oculomotor nerve as they passed forwards through the mid-brain.

SUMMARY.

Right hemiparesis with sensory disturbances conforming to the thalamic syndrome in a man aged 50. Later widespread ocular palsies occurred and death resulted after a total course of ten months.

Giant-cell glioma affecting the inferior part of the internal capsule and the lateral mesencephalic area. Expansion medially (thalamus, tegmentum) and laterally (lenticular nucleus). No immediate primary relation to the ventricular wall.

Case 2.—E. B. aged 43, a single woman, was admitted to the National Hospital under Dr. Gordon Holmes, on March 1, 1937.

For many years she had held a responsible post as a head saleswoman and until one week before admission her health had been good. Then quite suddenly, she began to complain of feeling excessively tired and she found herself continually yawning. This fatigue grew worse and she became unusually sleepy. Four days before admission to hospital she became aware that her left hand was weak. At the same time she thought that the right corner of her mouth had become drawn up During the course of the next two days the weakness of the left arm became so great that she was scarcely able to withdraw it from beneath the bedclothes and movements of the fingers were quite impossible. On the morning of the day of her admission to hospital she found that the left leg had become rather weak and she was walking with a limp. To direct questions she said that she had been sleeping very heavily for about a week and she had no difficulty in sleeping for ten or eleven hours together. She denied ever having had any headache or pain elsewhere. There had been no disturbance of vision. The menses were regular and the last period had occurred about a fortnight before admission.

Examination.—March 1, 1937: The patient was a well-nourished, well-preserved woman. A degree of ptosis gave her a rather sleepy appearance, but she was alert and co-operated fairly well. Orientation was correct and there was no gross defect of memory. There was no apraxia in the unaffected (right) arm. She was right handed.

Cranial nerves.—Smell, taste and hearing normal. Vision $\frac{6}{6}$ in each eye. The visual fields were full to confrontation tests and there was no attention defect or visual disorientation. The fundi were normal.

The external ocular movements were full and there was no nystagmus or diplopia. The pupils were unequal (right 4 mm., left 3 mm.) and slightly irregular in outline.

They were fixed to direct and consensual light but reacted moderately well on convergence. There was a moderate bilateral ptosis, rather more marked on the left, with overaction of the frontalis.

There was a doubtful hypoalgesia on the nose which seemed rather more definite on the left. Sensibility to light touch was normal. Both corneal reflexes were present but the left was less brisk than the right. Marked weakness of the left lower face was well brought out in ordinary conversation. It was very little marked when she smiled or laughed. When the mouth was maintained widely open the left arch was not so well preserved as the right.

The remaining cranial nerves were normal.

Motor functions.—Upper limbs: There was no wasting, fibrillation or involuntary movement. The left arm lay helplessly by her side and was quite toneless. Enough power remained at the shoulder to maintain the arm outstretched for perhaps a second. There was trace of voluntary flexion and extension at the elbow, but the paralysis was complete below the elbow. Firm grasping with the right hand caused feeble associated flexion of the left arm. The functions of the right arm were entirely normal. The lower limbs showed neither wasting nor fibrillation. There was a very slight hypertonus of the left leg. Power was slightly reduced in all muscle groups of the left leg. There was no inco-ordination. The functions of the right leg were normal. The sphincters were unaffected.

Reflexes: Both ankle-jerks were absent, the other tendon-jerks were normal. On the left the superficial abdominal reflexes were absent and the plantar response was extensor.

Sensation was everywhere normal for prick, touch, temperature discrimination and vibration. Appreciation of posture and direction of movement was normal in the fingers and toes. Discrimination of compass points was normal in the hands and feet.

Cardiovascular system: Heart enlarged to the left, the apex beat being six inches from the mid-line ; a long systolic murmur at the apex was conducted upwards over the aortic area. No diastolic murmur was heard. Pulse 70. Blood-pressure 90/65 mm. Hg. The other systems were normal.

Progress.—March 2, 1937: Slight sensory loss was observed in the left hand.

Discrimination of compass points was faulty and there was slowness in identifying common articles placed in the left hand.

March 15: The pupils were more irregular than on admission and totally inactive to light. The left leg was slightly hypertonic. For the first time it was possible to demonstrate a slight hypoalgesia on the left limbs and trunk. There was marked loss of postural and 2-point discrimination in the left hand and foot, the hand being the more affected.

March 30: She complained of headache and vomited once. There was blurring of the nasal halves of the optic discs and marked inability to look upwards. On confrontation there was slight limitation of the left homonymous fields. From this time she slowly became demented, but there were brief intervals in which she was able to recognize her friends. She suffered from considerable headache. The fundi remained unchanged and, although the discs were blurred, no measurable swelling appeared.

In general the signs remained unchanged ; the hemiplegia gradually became spastic until the rigidity of the left arm and leg were intense and the superficial sensory loss became more marked. However, the loss of sensibility to prick never became complete, and to the end she vigorously resented strong stimuli. At no time did she complain of anything resembling spontaneous pains. The "thalamic response" was never detected, but it must be remarked that for many weeks before her death a proper sensory examination was impossible. The condition of the pupils and external ocular movements during the time she was under observation were of particular interest.

April 12: Both pupils were totally inactive to light, the left pupil reacted only slightly on convergence ; the right was fixed. Paralysis of upward conjugate movement was first noted on March 30 and it was then complete. However, twelve days later there was some slight ability to elevate the eyes. Conjugate paralysis was again complete after a further two weeks, and remained so until she died. The power of convergence was lost about the beginning of May, and from that time until her death in June her eyes appeared to be entirely immobile. The size and shape of the pupils varied considerably from time to time. At times they were equal in size, more often the right was slightly the larger. In the last two weeks of her life they became moderately dilated, and the right was permanently rather the larger. The degree of irregularity also showed great variability from day to day. Perimetry was carried out shortly after admission and the fields were full. Later a left homonymous defect was detected, and confirmed on numerous occasions but her condition did not allow then of perimetry. The cerebrospinal fluid was examined on March 2. It was under an initial pressure of 120 mm. of water. It contained 0·180 per cent. of total protein but otherwise showed no abnormality. The Wassermann reaction was negative in blood and fluid.

Post-mortem examination.—The body of a very wasted, middle-aged woman. No external signs of disease. *Brain*: Arteries healthy. There was no swelling of the pons or mid-brain, but on examining the thalamus on the two sides after incision of the corpus callosum that on the right was definitely the more bulky. On incision a rounded mass of tumour was seen in the right thalamus. There was no significant lesion in the spinal cord or viscera.

On section of the brain in the horizontal plane the cortex in the calcarine region on both sides was found to be shrunken, brownish and softened. There was no evidence of thrombosis or other disease of either posterior cerebral artery. There was a greyish soft area in the mid-brain in the region lateral to the red nucleus and central grey matter. The tumour was a soft rounded or oval fairly defined brownish mass extending through the thalamus from near its upper surface down to the tegmental region of the mid-brain on the right side. It was not available for study in its entirety as portions had previously been removed for routine pathological examination. From what remained it could be seen that the tumour occupied the whole of the lateral part of the thalamus and appeared to invade to some extent the internal capsule. The medial part of the thalamus appeared less invaded. The anterior nucleus appeared quite free from growth. It was impossible to delimit the tumour more exactly for the reason already stated.

Microscopical examination.—The tumour was composed of small rounded cells with rather irregularly sized nuclei. There were very numerous and thin-walled vessels in the tumour and numerous threads of reticulum and collagen in the matrix. Vessels of medium size were cuffed with tumour cells. The cells showed many mitoses, chiefly irregular, and there was a great tendency to degeneration. The appearances were those of meningeal sarcomatosis. There was no resemblance to a glioma.

In the calcarine cortex the nerve cells had disappeared, leaving an area of gliomesodermal reaction in the deeper layers and a swelling and proliferation of macroglia in the surface layers.

From the remaining part blocks were imbedded in celloidin and serial sections (every 25th section) were stained with thionin. In the basal ganglia the tumour occupied the larger part of the lenticular nucleus and the ventro-lateral zone of the thalamus, replacing the whole sector of the intervening internal capsule. Only a small (dorsal) part of the globus pallidus and the dorsal and lateral zones of the putamen were preserved. The tumour had obviously destroyed parts of the ansa lenticularis. The substantia innominata (Reichert), the nuclei of the tuber and the paraventricular nucleus were preserved. The medial areas of the thalamus were not invaded. In the dorsal part of the medial nucleus there was a small area of an apparently fresh softening. In the central third of the pes pedunculi there was an area of tumour which extended through the zona reticulata and pars dorsalis of the substantia nigra into the field of the medial lemniscus. In its neighbourhood, in the substantia reticularis, near the central grey matter, there was a small area of recent softening. It could not be determined whether or not the mesencephalic area of tumour was in connection with the main part of the tumour. In the central grey matter, around the aqueduct, there was a diffuse proliferation of capillaries and glia.

SUMMARY.

Clinically: Left hemiparesis and, later, severe sensory loss in a woman aged 43. Reflex iridoplegia occurred early in the disease which proved fatal after a course of three months. Signs of increased intracranial pressure and dementia occurred late in the disease.

Anatomically: Round cell sarcoma of the internal capsule expanding in both directions ; into the thalamus from the periphery towards the ventricle, and into the lenticular nucleus. Area of growth in the ventrolateral area of the mid-brain. Bilateral infarction of the visual cortex.

COMMENT.

These two cases have this in common that distinct focal symptoms, such as are met with in other cases of capsular or thalamic lesions, were the initial symptoms and dominated the clinical picture almost to the end. The first patient suffered from contralateral hemianæsthesia and hemiparesis; the second developed first a hemiplegia and, soon afterwards a hemianæsthesia; in both the pupils were fixed to light. Leaving aside for the present this last-mentioned symptom and those which developed at a late stage, we may accept the predominant and initial symptoms (hemiparesis, hemianæsthesia) as typical of a capsulothalamic lesion. Neither of these cases can be regarded as a primary thalamic tumour. They occupied part of the internal capsule, the fillet system, the lateral and ventral mesencephalic areas and extended in two directions: medially towards the 3rd ventricle and laterally towards the lenticular nucleus. In other words, whatever the site of origin of the tumour, whether in the lateral or ventral mesencephalic areas or in the internal capsule contiguous to the thalamus, it is clear that the thalamus was first invaded in its lateral and ventral regions.

The first case was a typical giant-cell glioma (Roussy and Oberling) and it is noteworthy that the duration of life was longer than in the other cases. The second case was more interesting from a histological point of view. With its round cells, which either spread as a compact growth or permeated the Virchow-Robin spaces, it resembled closely the cases of primary round-cell neoplasms of the brain (Fried 1926, Környey 1934, Scheinker 1936, Mage and Scherer 1937). It is remarkable that the four similar cases reported by previous authors also occupied the basal ganglia, probably arising from the meninges of the base. As in this case hemiplegia was the first symptom it is conceivable that the tumour originated in the pes pedunculi and expanded in upward direction. If this is so it might explain the early loss of pupillary reactions.

INTRINSIC THALAMIC GLIOMAS.

Case 3.—T. C., a man aged 64, was admitted to the National Hospital (Dr. Gordon Holmes) on September 9, 1932. The details of the history were confirmed and supplemented by his wife.

In April, 1932 he was suddenly discharged from his employment because of business depression and this caused him great anxiety. Up till that time his health had been good although he had always been of a "nervy" disposition. From this time he became unusually tense and was obviously brooding over his trouble but no certain mental or physical defect was noted until some six weeks before admission to hospital when he noticed a gradually increasing weakness of the right side of the body affecting the upper limb rather more severely than the lower. At about the same time he began to complain of "coming queer" in his head and that the right arm and leg felt cold. His wife first realized that he was seriously ill when she discovered that his handwriting had degenerated into a scrawl and that he was unable to handle a pen. About August 20 he began to suffer from severe headaches. These he attributed to constipation. They were accompanied by nausea but he never vomited. He was himself aware of a deterioration of memory and was aware of, although not distressed by, his inability to recollect the details and chronology of his illness. He had always been a restless sleeper taking a long time to get off to sleep. Latterly this had not been so and in addition he was often drowsy by day. No disturbance of speech had been noted. No fits had occurred. He was right handed.

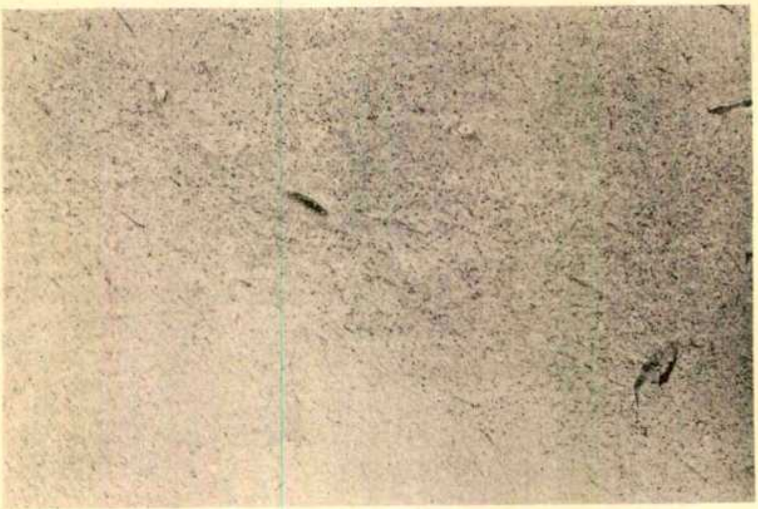

FIG. 2.—*Case 3.* The lateral nucleus is invaded by tumour growth which here stops short accurately at the border towards the internal capsule. It is noticeable even at this magnification that the nerve cells in this area are preserved. (Nissl. × 14.)

Examination.—September 9, 1932: The patient was a tall rather thin and ill looking man who suffered from frequent and severe headache. He was inclined to be drowsy but, when roused, was quite alert. Mentally he showed a striking loss of memory together with some inattention. As noted above he gave a disjointed and incomplete history. He answered incorrectly or not at all such questions as "What hospital are you in?" "When and where were you born?" "When were you married?" He did not retain an address or any digit of a series of 7. Judgment and insight were certainly impaired, for, despite professions of concern for the future of his family, he made flippant replies when asked what would he do when cured. His attention could not be held for more than a few seconds. He smiled vacantly from time to time. There was no aphasia or apraxia.

His handwriting was only just legible but the paresis and sensory loss in the right hand were sufficient to account for this.

Vision was $\frac{6}{6}$ in each eye. The fields were full on confrontation and perimetry. The optic discs were thought to be a little blurred and the retinal veins somewhat overfull, but these observations were not confirmed by Mr. Williamson-Noble when he examined the fundi a week later. The pupils were equal (4 mm.), slightly irregular and reacted briskly to direct and consensual light and in convergence. The external ocular movements were full in all directions. There was no nystagmus, squint or diplopia. There was a very questionable bilateral ptosis. The jaw deviated slightly to the right when opened against resistance. There was definite weakness of the right lower face which was accentuated by sustained voluntary movement. Sensibility on the face was normal. The corneal reflexes were present and equal although somewhat sluggish. The remaining cranial nerves were normal.

There was a mild right hemiparesis. The loss of power was somewhat greater in the leg than in the arm. The posture of the right arm was very poorly sustained. Tone was normal in the arm, but was slightly increased in the right leg. There was a very gross inco-ordination in the right arm and leg which was independent of vision.

On the right the tendon-jerks were exaggerated, and there was ankle-clonus ; the superficial abdominal reflexes were absent and the plantar response was extensor. On the left the reflexes were normal except for an equivocal plantar response.

Sensation was difficult to assess. He was incapable of co-operating for more than a few seconds. Perception of light touch and vibration appeared to be normal. Pin-prick was perhaps a little dulled over the right hand, elsewhere it was normally felt. Sense of position and passive movement appeared to be altogether absent in the right extremities but were normal on the left. Compass tests were attempted but the patient persisted in repeating the same answer.

Examination of the other systems did not reveal any abnormality. Pulse and temperature remained within normal limits throughout. The urine was normal in constitution and amount. The *cerebrospinal fluid* was examined on September 9, 1937. It was under a pressure of 100 mm. water. There were three small and medium sized mononuclear cells per centimetre. The total protein was 0·130 mg. per cent. and the globulin test was weakly positive. In other respects the fluid was normal. The W.R. was negative in blood and fluid.

Stereoscopic radiograms of the skull did not show any abnormality.

Progress.—September 22, 1937 : He was distinctly more alert and free from headache (daily enemata of 50 per cent. magnesium sulphate had been given since September 15). With the eyes closed he had no notion of the position of the right arm and leg. Slight hypoalgesia and hypoaesthesia was confirmed on the right side, particularly in the upper extremity.

September 29 : There was a marked increase in the mental symptoms and a severe nominal aphasia. Power was still very good on the right side although a little diminished by comparison with the left. The inco-ordination on the right side was even more marked than on admission. It resembled cerebellar ataxia. The right plantar response was strongly extensor, the left was doubtful.

After this the patient's condition steadily deteriorated and death occurred from a terminal pneumonia.

Post-mortem examination.—The body of a very thin elderly man. No external sign of disease. Brain only removed. The dura was tense and the convolutions flattened. On opening into the ventricles, which were considerably dilated, a large softened tumour bulged into the left ventricle in the region of the basal ganglia.

It pushed the bend of the ventricle backwards behind that on the right side. Post-mortem examination of the internal organs showed bronchopneumonia, healed nodular tuberculosis of the apices, atheroma of the aorta and a double renal pelvis on one side.

On section of the fixed brain in the coronal plane a tumour was seen in the left basal ganglia occupying an area which extended from the level of the pineal body posteriorly to the level of the infundibulum anteriorly. In its anterior and lower parts it was white and firm causing a diffuse swelling of the thalamus. The upper and posterior parts were hæmorrhagic and diffusely brownish red. Here the tumour pushed the middle part of the lateral ventricle and, further back, pressed across the mid-line. It appeared to involve almost the whole of the left optic thalamus. In the middle part, where the tumour was soft and hæmorrhagic, a very small rim of the thalamus along the medial (ventricular) surface seemed to be preserved. In its anterior part the internal capsule seemed to be infiltrated to a small extent.

Microscopical examination.—The tumour was composed of large cells with one or two peripherally placed nuclei and numerous fine processes. It was very degenerated in its upper part but very few multinucleated cells were seen in it and no mitoses were visible. It appeared to be a large celled astrocytoma. In serial sections (53 sections, 20μ, Nissl) the tumour was first seen at the anterior tip of the thalamus compressing, but not invading, the adjoining part of the caudate nucleus. There was an area of tumour infiltration around the vena terminalis. In large parts of the lateral nucleus and the medial nucleus in the anterior planes the tumour occupied the whole of the thalamus but the nerve cells were still seen in these areas (fig. 2). More caudally the tumour again consisted of vast degenerated areas in which nothing of the destroyed tissue was visible. It expanded laterally into the internal capsule in its posterior third and in its sublenticular part. Dorsally and medially it extended into the pulvinar which was entirely replaced by tumour tissue. Here it expanded laterally into Wernicke's field and infiltrated the medial fifth of the lateral geniculate body in its dorsal part. Ventrally it did not expand into the region of the vegetative hypothalmic nuclei neither did it reach the mid-brain caudally. In the mesencephalic level a considerable zone of the ventral nucleus and of the medial nucleus (nucleus reuniens, Malone) was preserved. The tumour nowhere came into the area of the eye muscle nuclei or of the red nucleus. On the lateral and ventral surfaces of the pulvinar the tumour expanded into the wall of the inferior horn, compressing and partially infiltrating the ventricular surface of the hippocampus and the white matter surrounding the inferior horn. It stopped short at the U-fibres of the cortex of the temporal lobe. The basal ganglia on the right side were normal apart from a zone of subependymal gliosis which separated the right thalamus from the ventricle. Trial sections from the frontal lobes and cerebellum, stained with Nissl and Scharlach R, were normal.

SUMMARY.

Clinically: A man aged 64 showed a rapidly developing right hemiparesis with pronounced sensory loss. Mental deterioration occurred early and became deep before death which occurred some six months after the onset of symptoms.

Anatomically: There was a large celled astrocytoma, with a marked tendency to degeneration, which occupied the left thalamus with the exception of a small area in the posterior planes of the medial and ventral nuclei. The mid-brain and the eye muscle nuclei were intact. The internal capsule in its posterior third and sublenticular portion were partially infiltrated. There was also an infiltration of the white matter surrounding the inferior horn and of the hippocampus on its ventricular surface.

Case 4.—W. G., a man, aged 67, was admitted to the National Hospital under Dr. Gordon Holmes on April 4, 1937.

The history was obtained from a son who said that his father had always had good health until the onset of his present illness. In the middle of February, 1937, some six weeks before admission to hospital, he caught influenza. He took to his bed and seemed very weak. He was a little "light headed," but no attention was paid to this as it had often been noted before if he chanced to be feverish. However, when the fever remitted in the course of a few days these mental symptoms did not clear up. He continued to be unusually weak and his mental condition was abnormal. In describing the mental state as "light headed," the son meant a childish and rather fatuous manner. His speech was perfectly intact but his remarks were constantly silly and irrelevant and the family could place no reliance on his statements. He continued in much the same state until a week before admission to hospital and then speech began to fail rapidly. This was first apparent by a failure to select the proper word but, within a few days, he was quite unintelligible and incapable of reading or writing. From the beginning of his illness he had been unusually sleepy but in the last few days this had become more marked. Headache first appeared at the time when the drowsiness increased but there was no vomiting. On the day of admission there were several outbursts of great excitement and violence. He seized anything at hand to throw at his wife and terrified the whole family. Vision was unaffected, at any rate up to the onset of aphasia. He had been incontinent of urine and fæces for one day.

Examination.—April 4, 1937: A well-nourished man in no evident pain and quite alert. He was right handed. The presence of an almost total aphasia made thorough examination difficult. His speech was unintelligible, being nothing more than a string of unconnected words. He was unable to read or write and he did not appreciate pantomime. He showed imperfect recognition of common articles. When handed a pencil he had no notion of how it should be held. There was some degree of apraxia. When given a box of matches he at length recognized its nature but it was only after fumbling for several minutes that he succeeded in extracting and striking a match. He showed no distress at or insight into his condition but smiled constantly.

Cranial nerves.—Smell apparently normal. Visual acuity not determined. He frequently shut his left eye, particularly if he wished to look at anything; and he had a marked disinclination to look towards the right. On confrontation there was a considerable right homonymous hemianopia, but perimetry could not be used. The fundi were normal. The external ocular movements were full, although there was disinclination to look to the right. There was no obvious squint, ptosis, en- or exophthalmos. The pupils were equal (3 mm.), very slightly irregular in outline and almost fixed to direct and consensual light. Convergence could not be obtained. There was a pronounced weakness of the right lower face which was very noticeable in ordinary emotional play. The tongue came out straight. There appeared to be some diminution of sensibility to prick over the right half of the face but the corneal reflexes were present and equal.

The remaining cranial nerves were normal.

The right arm and leg were moved less than the left. When support was withdrawn from the outstretched arms the right fell away at once. Voluntary movements were slightly weaker on the right. There was a peculiar irregular and rather coarse tremor of the right arm. It was only present when the limb was unsupported and, if anything, was more palpable than visible. More exact tests of co-ordination could not be applied. The tendon-jerks were slightly increased on the right and there was clonus of the right foot. All the abdominals were absent. Both plantars were flexor but the right toes tended to fan. To crude tests with pin-prick there was a definite hypoalgesia on the right trunk and limbs. Examination of other systems did not disclose any abnormality, except for a moderate arteriosclerosis. The blood-pressure was 170/120 mm. Hg. The urine was normal.

Cerebrospinal fluid: Pressure, 300 mm. water. Fluid yellow. Cells 25 per c.mm. (2 per cent. polymorphs, 10 per cent. large mononuclears). Total protein 0·40 per cent. Globulin test strongly positive. W.R. negative in blood and fluid.

Progress.—There was progressive deterioration. To exclude the possibility of a subdural hæmatoma trephine holes were made and the ventricles were tapped. The exploring needle encountered a solid tumour deep in the left hemisphere. He died one month after admission to hospital.

Post-mortem examination.—The body of an old man, rather thin, no external signs of disease. The brain only was removed. The dura was moderately tense but there was no evidence of cerebellar pressure cone. No softening of convolutions was visible externally but the left temporo-parietal region felt bulkier than the right, and on opening into the lateral ventricles, a brownish tumour mass was seen filling the left optic thalamus and projecting into the third ventricle. Its central part was gelatinous on section, and actual tumour substance appeared as a very thin layer. The tumour extended backwards from the optic thalamus to the occipital white matter external to the ventricle. Anteriorly it passed upwards to the superior surface of the thalamus, and laterally to the lenticular nucleus, leaving only a part of the ventral nucleus of the thalamus macroscopically intact. The exact extension in the hypothalamic region could not be defined in the material still available. In its lateral parts the tumour invaded large areas of the white matter. In the occipital lobe the growth stopped short beneath the U fibres of the cortex.

Microscopical examination.—In its undegenerated parts the tumour was composed of astrocytes of very varied size and shape, but with very well defined fibres forming a moss-like background. Many of the larger cells had large cell bodies but rarely more than one or two nuclei. Mitoses were only seen in the endothelial cells of the vessel walls. On approaching the degenerated areas the cell nuclei became pyknotic and many of them showed karyorrhexis. In these areas mitotic figures were seen. The tumour was an astrocytoma but with more tendency to polymorphism and degeneration than is shown by most tumours of this type.

In serial sections (45 sections, 20 μ, Nissl) the tumour extended from the anterior tip of the thalamus, including the anterior nucleus, to the posterior tip of the pulvinar. In its anterior levels it pushed a small preserved rim of grey matter into the ventricle and upwards towards the corpus callosum. In dorsal direction it stopped short at the vena terminalis, compressing to a certain extent the caudate nucleus but not invading it. In ventral direction it did not occupy the whole thalamus. The ventral nucleus was preserved in large part. Even parts of the lateral nucleus were preserved, or in some levels its nerve cells were preserved though invaded. Thus the tumour had not invaded the hypothalamic region or the mid-brain. Its chief extension was in a lateral and posterior direction. It occupied the posterior and inferior part of the internal capsule, the posterior part of the lenticular nucleus, and almost the entire white matter of the temporal lobe lateral to the inferior horn. Nowhere did it reach the cortex itself. Wernicke's field was partly invaded. For the most part the tumour was confined to the pulvinar and stopped accurately at its lateral and inferior borders. The lateral geniculate body itself was free. The tapetum, Gratiolet's radiation and the inferior longitudinal bundle were replaced by tumour tissue. The subependymal glia surrounding the vena terminalis was proliferated at levels where there was no actual tumour. Apart from this there was an even subependymal gliosis on the ventricular surface of the caudate nucleus.

SUMMARY.

Clinically: A man, aged 67, showed a rapidly developing mental deterioration which was followed by slight right hemiparesis with some sensory loss. Reflex iridoplegia was present early in the disease.

Anatomically this tumour was an astrocytoma, replacing almost the whole left thalamus, except for parts of the ventral nucleus. It had a tendency to grow along the ventricular wall and to expand in a posterio-lateral direction. Thus, apart from the thalamus, it had destroyed chiefly the secondary optic system, the internal capsule and part of the lenticular nucleus.

Case 5.—R. B., a man aged 63, was admitted to the National Hospital under Dr. Riddoch on February 8, 1937. By birth a Bulgarian he had lived in England since childhood and, until the onset of his present illness, had enjoyed excellent health. The following history was obtained from his wife:—

About one month before admission he first complained that his near vision had become poor. He went to a spectacle maker who gave him lenses but these did no good. Indeed he was rather worse off for he complained that, when reading, the print appeared double and to overcome this he acquired the habit of closing his left eye. At this time his family became aware of a slight change in his disposition. Previously he had been mentally and physically active but now he was slow and this slowness day by day became more evident. He was noticed to take an unusually long time in dressing and his replies to quite simple questions were delayed. First he lost the ability to write and his attempts at writing became a mere childish scribble. At this time he became unable to read. He was often seen with a newspaper in his hands but he never turned the pages and merely stared vacantly at whatever was before him. Soon after this his speech began to fail. His articulation was correct but he put his words together badly. At times however he spoke remarkably well. His memory had become grossly unreliable in the past two weeks. He never alluded to the distant past but recent happenings were hopelessly mixed up. His temper had become uncertain. For about two weeks he had been excessively sleepy. His gait was noticed to be slightly unsteady about a week before admission.

He did not veer to one side more than another. His general health seemed unaffected. His appetite was very good ; indeed better than usual. There was no loss of flesh. He had never complained of headache and when directly questioned, denied ever having had any. There had been no vomiting. For perhaps two weeks he had often been seen to play with his fingers, touching one after another with the thumb, now with one hand, now with the other. His wife thought that this was an imitation of one of the tests which his doctor had used.

Examination.—February 19: The patient was a spare elderly man, unable to give a history by reason of a severe dementia. To direct questioning he said that his eyes were wrong but in what way could not be ascertained and no admission of diplopia was obtained. He constantly screwed up his left eye. He explained that he first did this to overcome double vision but he would not say why he still did it. He was disorientated in time and space and he was quite unable to carry out the simplest mental arithmetic. There was no apraxia but he was slow and clumsy in using his hands. On one occasion he attempted to put some coins in what he imagined to be an inside pocket of his pyjama jacket. He was able to dress himself, but had to be reminded to get into each garment separately.

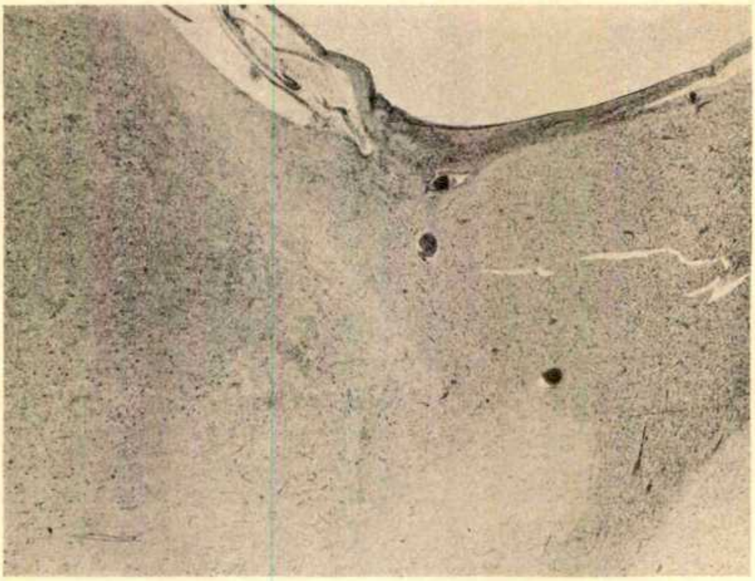

FIG. 3.—*Case* 5. The anterior border of the tumour coincides with the anterior border of the thalamus. The ganglion cells in these areas (lateral nucleus) are preserved. Note the subependymal gliosis over the ventricular surface of the caudate nucleus. (Nissl. × 12.)

He never spoke unless spoken to. His replies were correctly phrased and articulated but he was slow and halting and used as few words as possible. It was impossible to obtain a specimen of his handwriting. When given a pencil he held it for several seconds and then threw it down saying he could not see to write. He made the same excuse in explanation of his partial inability to read. When urged he read slowly and words of more than two syllables gave him great difficulty. When shown a series of common articles he misnamed several. He used the word pencil to describe a pocket torch, a fountain-pen and a penknife when these were shown to him in succession. Despite the dementia, co-operation was remarkably good provided commands were given in a simple direct form. He was right-handed.

He appeared to recognize but could not name any of the usual test odours (peppermint, cloves and camphor). The sense of smell was less acute in the left nostril. Vision approximated $\frac{6}{24}$ in each eye. The visual fields were full by confrontation tests and there was no attention defect or visual disorientation. Perimetric charts were not obtainable because of the dementia. The fundi were normal. Hearing was slightly reduced in both ears; Weber was not lateralized and air conduction was better than bone conduction on both sides. There was complete paralysis of upward movement of both eyes, both voluntarily and reflexly. The other external ocular movements were full and there was no nystagmus or diplopia. The pupils were small (2 mm. in diameter), equal and regular in outline. There was only the merest trace of contraction to direct and consensual light. There was complete

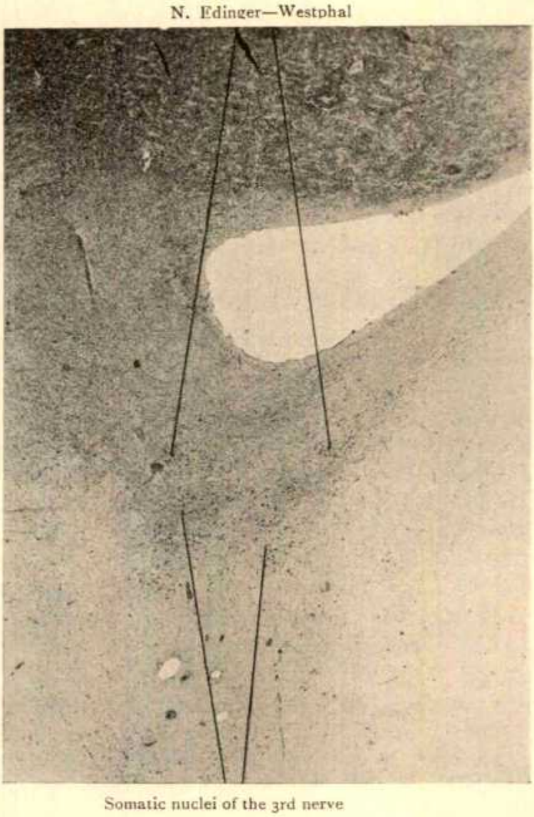

FIG. 4.—*Case 5.* Relation of the posterior margin of the growth to the eye muscle nuclei. (Nissl. Approx. × 13.)

inability to converge. There was no ptosis, en- or exophthalmos. The other cranial nerves were normal. Sensation on the face was intact, and the corneal reflexes were equally brisk.

There was no wasting, fibrillation or involuntary movement. Tone was natural in all the limbs and active movements were normally strong. There was no tremor or inco-ordination, and alternating movements were carried out equally well on both sides. His gait was slightly unsteady but no more to one side than the other. The tendon-jerks were present and equal upon the two sides. The superficial abdominal reflexes were all present and both plantar responses were flexor.

Pin-prick, light contacts with cotton wool, and temperature discrimination were normally and equally perceived on both sides of the body. Appreciation of passive movement and direction of movement was normal in all four limbs. Discrimination of two points was normal on the hands and feet. Firm pressure on the calves evoked a normal and equal response.

There was no sign of any cardiovascular disease. The vessels were healthy. Blood-pressure 115/70 mm. Hg. The other systems were normal.

The *cerebrospinal fluid* was under a pressure of 140 mm. of water. It contained 1 cell per c.mm., and the total protein was 0·09 per cent. In other respects it was normal, and the W.R. was negative in blood and fluid.

Progress.—His condition remained stationary except that, after a few days, the pupils became totally inactive to light, and on February 24 ventriculography was performed. It was considered likely that he had a neoplasm in or about the posterior part of the third ventricle and this assumption was supported by the ventriculogram which showed incomplete filling of the posterior end of the ventricle. The shortness of the history suggested that the neoplasm was invasive and therefore inoperable. He gradually passed into a comatose state and died on March 9. In the last few days of life the right arm became flaccid and motionless and he developed bilateral extensor plantar responses. Repeated examinations of the fundi confirmed the absence of papillœdema throughout the entire course of the disease.

Post-mortem examination.—The body of a wasted rather elderly man. No external signs of disease except burr holes for ventriculography. The brain only was removed. The dura mater was very adherent to the skull.

Brain tissue was seen to be herniated into the burr holes. There was, however, no other evidence of increased intracranial pressure. The posterior aspect of the mid-brain was seen to be swollen and white, especially on the left side, and the left optic thalamus was very firm and bulged into the third ventricle.

On section of the fixed brain the tumour appeared to be limited to the left optic thalamus and to involve practically the whole of this structure. It did not appear to involve the mid-brain except in a small area in the region of the left superior corpus quadrigeminum. It extended toward the medial wall of the posterior horn where it bulged the intact ventricular wall into the ventricle. Laterally it apparently invaded the internal capsule for a small distance but a large part of the lateral and ventral nucleus of the thalamus seemed intact. It extended through the massa intermedia into the medial area of the right thalamus. At its frontal end it seemed to stop short at the caudate nucleus.

Histological examination.—The tumour was rather polymorphous. In the most rostral levels (about the level of the anterior thalamic nucleus) there were a large number of oval cells in an indefinite matrix. They were uniformly dense and in some planes followed the direction of the myelin fibres. There were no mitoses.

The whole appearance at this level was rather like that of a diffuse pontine glioma. The character of the neoplasm changed considerably at the levels posterior to this. Here the density varied from place to place. There were areas of necrosis and pseudorosettes. At these levels indeed the tumour might have been classified as a glioblastoma. Even here, however, mitoses were very rare.

Blocks of the basal ganglia extending from the middle of the lenticular nucleus down to the caudal part of the red nucleus were imbedded in celloidin and serial sections were cut (every twenty-fifth section, Nissl).

Left side: The medial thalamic nuclei were entirely destroyed. In the posterior areas they were replaced by tumour tissue.

In the anterior levels (level of the anterior nucleus) the medial nucleus (dorsomedial nucleus) was invaded by tumour cells but the ganglion cells were preserved. The posterior and inferior parts of the medial nucleus together with the centre-median nucleus and nucleus arcuatus and nucleus semilunaris had disappeared. The lateral nucleus was preserved in the dorsal levels. In the lower parts and caudal two-thirds the lateral and ventral nuclei were either partially infiltrated by tumour or completely destroyed.

The anterior nucleus was preserved except for a slight gliosis at its postero-inferior edge. The mamillo-thalamic tract (Vicq d'Azyr) seemed intact. The pulvinar was completely destroyed.

In the posterior part of the third ventricle the tumour formed a bridge to the ventricular wall of the opposite side. The anterior part of the superior colliculus was invaded. The tumour extended with a long process along the medial wall of the inferior horn, and was attached to the cortex of the hippocampal area. A part of the cortex of the area glomerulosa (Economo) was destroyed by compression. The internal capsule was slightly invaded in its posterior part adjoining the thalamus. The zona reticulata was free to a large extent. In some parts the edge of the tumour coincided exactly with the border of the thalamus (fig. 3). The ventricular nucleus was free from tumour. Some cells of the globus pallidus were swollen with eccentric nuclei. The nucleus of Edinger showed a marked gliosis on the left side and a slight one on the right. The somatic nucleus of the 3rd nerve was intact. The left nucleus commissuræ posterioris (Darkschewitsch) was infiltrated by tumour cells (fig. 4). The substantia innominata of Reichert was intact. The mamillary bodies, the nuclei of the tuber, and the supraoptic nuclei were intact. A dorsal (accessory) part of the paraventricular nucleus was slightly infiltrated. The corpus subthalamicum and the lateral geniculate body were intact.

Right side.—The tumour had invaded the massa intermedia and medial areas of the adjoining thalamus. The ganglion cells in these invaded areas appeared intact. The subependymal glia separating the medial thalamic nucleus from the ventricular wall had proliferated to a marked extent.

Trial sections from various parts of the cortex did not reveal any abnormality.

SUMMARY.

Clinically: A progressive dementia in a man aged 63 ending in death within two months of the first symptoms. Reflex iridoplegia was an early sign. Motor and sensory signs were absent till within a few days of death.

Anatomically: Diffuse glioma of the left thalamus spreading along the ventricular wall across the massa intermedia to the opposite side, and extending to the most anterior part of the aqueduct and along the inferior horn. Its mode of expansion was such that the latero-ventral thalamic areas were obviously the last to be affected.

Case 6.—E. E., a woman aged 44, was admitted to the National Hospital under Dr. C. P. Symonds on September 10, 1937.

The family history was uneventful. The only noteworthy detail in her past medical history was a questionable history of slight Graves' disease in 1921. She had always been of an intensely active disposition, "heading for a breakdown for several years." Her pulse was habitually rapid.

On June 14, 1937 (i.e. some three months before admission) she had what seemed an ordinary attack of influenza and was in bed for three days with malaise, catarrh, aching in the limbs and some fever. When she got up her pulse was rapid and she was put on Bellergal. Three days later she complained that everything seemed out of focus and when reading she was shutting one or other eye to stop the lines running together. The pupils were noticed to be dilated. She found tennis impossible as she was always missing the ball. At this time she became unusually drowsy and she could sleep at any time of the day, and this symptom had been present to some extent ever since. Early in July she had one severe bursting headache and ever since she had complained of a constant buzzing over the head.

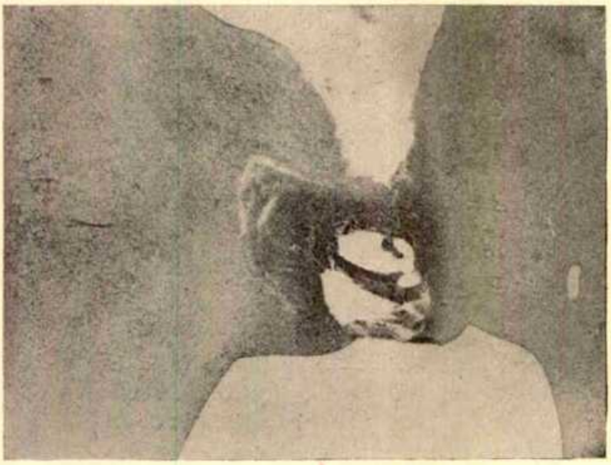

FIG. 5.—*Case 6.* The massa intermedia is occupied almost symmetrically by tumour tissue. (Nissl. × 10.)

A tentative diagnosis of encephalitis lethargica was made. Towards the end of July there was a severe attack of giddiness. Since then she had often felt dizzy and unsteady. In July and August headaches became more frequent, and she felt a pressure at the back of her neck. Six days before admission she began to vomit, and this lasted for three days. The headache was now less severe. She stated that her hearing had grown much worse but her husband thought it still very good. Her memory had been poor for some weeks, she could not concentrate and was hazy about dates. No change in temperament was admitted. Her speech was unaffected. No fits or faints had occurred. Libido had been failing for two years and absent for the past year. The menses were scanty and rather irregular.

Examination.—A thin woman weighing only 7 st. She was unable to give a history and could neither date the onset of her symptoms nor give their evolution. Her memory, especially for recent events, was very bad and she had forgotten events of the past week. She was very confused. She retained six and sometimes seven digits. She could not subtract seven from hundred. Marked inattention and disorientation were present. She was rather drowsy but co-operated fairly well when stimulated. Her mood was normal but she had very little insight. Her speech was normal.

Cranial nerves.—Smell normal. V.A.R. $\frac{6}{9}$. V.A.L. $\frac{6}{9}$. Fields full on confronta-tion with a 3 mm. white object. Fundi normal. The pupils were equal and of moderate size, slightly irregular in outline and displaced a little inwards ; absolutely inactive to light but still reacting, though feebly, on convergence. Convergence was almost absent. Slight convergent squint was present at rest with constant nystagmoid jerking, the quick component being inwards. The eyes were directed a little downwards and there was complete paralysis of conjugate upward movement, which persisted when the head was bent forwards. Conjugate downward movement was slightly limited. There was marked weakness of both lateral recti, the right more than the left ; and slight weakness in conjugate movement to the right ; the left eye did not quite reach the inner canthus. There was no nystagmus on movement, no ptosis or proptosis. She did not complain of diplopia at the time

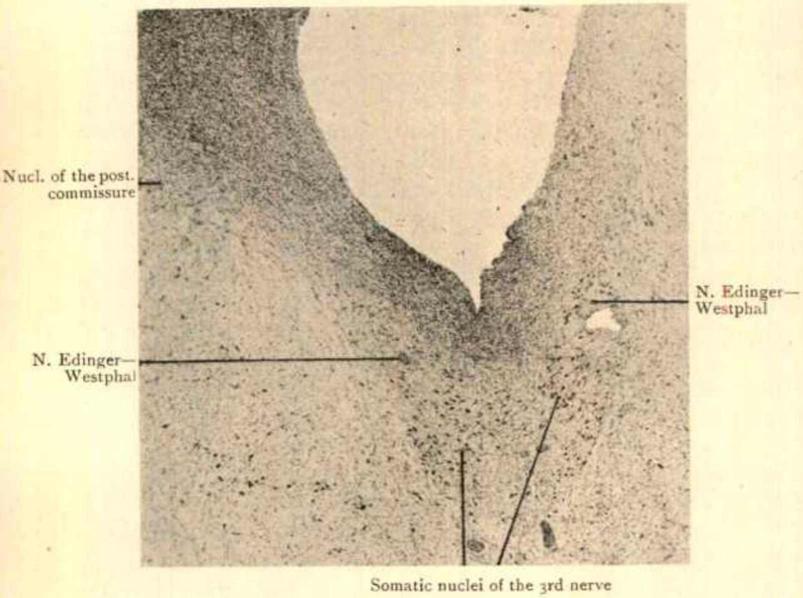
Nucl. of the post. commissure
N. Edinger—Westphal
N. Edinger—Westphal
Somatic nuclei of the 3rd nerve

FIG. 6.—*Case 6.* Relation of the posterior margin of the growth to the eye muscle nuclei. (Nissl. × 18.)

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of examination. There was no deafness. The remaining cranial nerves were normal.

Apart from some general asthenia there was no abnormality of the motor system. The tendon-jerks were all brisk. The superficial abdominals were feeble. Both plantar responses were indefinite but there was much voluntary movement. Sensation was entirely normal.

General examination.—Temperature rather low, 97·4° F. Pulse about 70-80, blood-pressure 115/90. *Urine* normal except for a trace of albumin. S. G. 1022. *Cerebrospinal fluid* (September 13, 1937) initial pressure 110—140 mm. water. The fluid was clear and colourless and no cells were seen. The total protein was 0·120 per cent. and the globulin tests were weakly positive. The W.R. was negative in blood and fluid.

Progress.—September 16: There were marked apathy, indifference, lack of insight and a general inattention. The latter was so marked that she appeared deaf, but was not really so. Dr. Symonds diagnosed a mid-brain tumour in the neighbourhood of the pineal and decided against operation.

September 30: General condition worse; she was very drowsy; and complained of frequent headaches but always in a casual indifferent way. She vomited often, especially in the early morning. No change in the physical signs was found.

October 5: She seemed in her usual state at 8 p.m. but was found in coma at 10.30 p.m. and died in the early hours of the following morning.

Post-mortem examination.—The body of a rather thin small middle-aged woman. No external sign of disease. Only the head was examined. The bones of the vault were very thin but there was little evidence of erosion of the inner table. Dura fairly tight but no great flattening of convolutions and no evidence of pressure cones. There was slight bulging of the infundibular region, and some distension of the lateral and third ventricles. On cutting through the splenium a fairly well defined tumour, reddish-brown in colour, was seen growing from the upper part of the quadrigeminal plate. It was attached to the right optic thalamus and appeared to infiltrate the posterior part of the left thalamus fairly deeply. The tumour occupied almost the whole of the anterior quadrigeminal bodies, leaving only a part of the left one and a small rim of the posterior commissure intact. It pressed on the right pulvinar and seemed to occupy the right habenular area. From there it expanded into the left side occupying the left pulvinar, the medial posterior parts of the left thalamus, and the centre-median nucleus at about to the level of the massa intermedia. The ventral nucleus seemed to be compressed but not infiltrated, the lateral nucleus and anterior part appeared intact. The internal capsule, the pes pedunculi, the red nucleus and the substantia nigra were also macroscopically intact.

Histological examination.—The tumour was very cellular and consisted of bipolar cells with oval rather elongated darkly staining nuclei and very ill-defined cell bodies. Many multinucleated cells of larger size were present, and some of these had ring nuclei or degenerated masses of chromatin, but no definite mitoses were seen. There was very little evidence of degeneration in the tumour.

In serial sections (20 μ, Nissl, every 25th section stained) the tumour began caudally at the caudal end of the quadrigeminal plate which was occupied almost completely. Within the quadrigeminal plate the tumour was practically symmetrical and extended ventrally no further than the most dorso-lateral tip of the oculomotor nuclei. Further forward it became asymmetrical.

On the left it expanded from the anterior colliculus forward and outward into the pulvinar which was for the most part replaced by tumour tissue. The whole of the medial nuclei of the thalamus, and the nucleus arcuatus, nucleus semilunaris, and centre-médian nucleus were replaced by tumour tissue.

The ventral nucleus was partially infiltrated. The lateral nucleus was only invaded to a slight degree; its main part was intact. The anterior nucleus was intact. In its rostral parts the tumour became gradually smaller and was confined to the areas of the medial nucleus which immediately adjoin the ventricular wall.

Orally it ended within the massa intermedia where it had an almost symmetrical position extending a little to both sides (fig. 5). In its caudal parts it extended latero-ventrally into the mesencephalic part of the medial lemniscus.

More orally it broke through the border of the ventral nucleus into Forel's field H and the zona incerta. It also broke through the lateral border of the pulvinar into Wernicke's field. The lateral geniculate body was free. The tumour touched the fronto-lateral tip of the red nucleus, and infiltrated the nucleus of the posterior commissure (Darkschewitsch) (fig. 6).

On the right the tumour extended from the anterior end of the superior colliculus into the medial areas (nucleus reuniens of Malone). Along the wall of the 3rd ventricle a small process passed forward but did not reach the massa intermedia to rejoin the tumour from the other side. Because the thalami had been torn apart it could not be certainly decided whether or not there was a bridge across the ventricle between the tumour on the left and that on the right.

SUMMARY.

A woman, aged 44, who showed progressive dementia and ocular disturbances over a period of four months. Motor and sensory signs were absent.

Anatomically: Diffuse glioma with symmetrical anterior and posterior limits (massa intermedia and quadrigeminal plate). In between these two limits it expanded chiefly to the left. The localization of this tumour was very similar to that of Case 5 except that here there was no extension along the inferior horn of the lateral ventricle.

COMMENT.

Clinically these cases were characterized by the fact that symptoms of mental impairment such as inattention, disorientation, confusion, emotional disturbances (Case 4), and sleep disturbances (Case 5), together with iridoplegia, dominated the clinical picture, and that, on the other hand, marked sensory and motor focal signs (hemianæsthesia, hemiplegia) were late in onset or poorly developed (Cases 3 and 4) or completely absent (Cases 5 and 6).

Case 3 is not easily distinguishable from the two cases in Group I except that mental impairment and drowsiness dominated the picture from the very beginning. This case stands in between the cases in the first group and the last two cases in which focal symptoms, except the eye symptoms, were almost completely absent ; the picture in fact was that of a progressive mental deterioration combined with fixed pupils.

Anatomically these gliomas have produced a final picture of grossly irregular invasion and destruction. Nevertheless they have some important features in common which justify their consideration as forming a single group. All of them were related to the ventricular wall ; none of them extending in rostral direction further than the vena terminalis. In the opposite direction they extended into the tegmentum of the mid-brain, involving the iter and the adjacent nuclei (Cases 5 and 6), and along the wall of the inferior horn (Cases 3, 4 and 5). This relation to the ventricular wall and the adjoining areas might be explained as secondary invasion by a tumour of the depth of the hemisphere. However, a comparison of the areas of complete tumour growth, either degenerated or undegenerated, with the areas in which the preserved nervous structures were evenly infiltrated by tumour cells, makes it clear that all these tumours had originated medially somewhere near the ventricular system and that they had expanded from there laterally into the hemisphere. Thus the internal capsule in its posterior third and sublenticular part, the white matter surrounding the inferior horn (Cases 3, 4 and 5), the subthalamic zone in Forel's field H near the body of Luys, and Wernicke's field lateral to the pulvinar were invaded. As far as the thalamus was concerned it was striking that the lateral and ventral nuclei were invaded but showed intact nerve cells or were in part completely free. This was most striking in Cases 5 and 6, and it is noteworthy that these were the cases in which sensory symptoms were entirely absent. There was an obvious tendency for the growths to stop short at the borders of grey or white matter so that the edge of the tumour coincided with the border of the thalamus (figs. 3 and 4). This, however, was only observed where the infiltration was recent and the invaded structure was not yet destroyed. At a more advanced stage the tumour masses expanded irregularly but the border towards the caudate nucleus at the vena terminalis was, even then, fairly well preserved (fig. 3). There was a subependymal gliosis in other parts of the ventricle where there was no actual gliomatous tissue. In none of these cases were the so-called " vegetative " nuclei of the hypothalamus invaded. Only in Case 5 a small dorsal accessory part of the paraventricular nucleus lay within the marginal zone of the growth.

CASES IN THE LITERATURE.

Few cases in the earlier literature are described fully. Usually they are mentioned as "Glioma of the thalamus" or "tumour of the third ventricle" or "glioma of the basal ganglia," and the anatomical diagnosis is briefly stated. Nevertheless an attempt was made to find similar clinical and anatomical features in order to discover, if possible, the typical features of such cases.

Mott (1898) remarked that tumours of the 3rd ventricle may be mistakenly diagnosed as "general paresis." Henneberg (1905) stated that tumours of the 3rd ventricle do not produce any focal symptoms but marked mental disturbances of a variable character. Pfeifer (1910), in his paper on psychic disturbances occurring in tumours of the brain, described three cases of glioma of the basal ganglia. Two of them were confined to the thalamus, in one the corpus striatum was invaded and there was adjacent softening. In all three cases there was a combination of severe mental impairment and disturbance of the pupillary reflexes so that the picture was similar to that of general paresis. Pfeifer, from a study of 86 cases of cerebral tumour, came to the conclusion that the mental symptoms occurring in tumours of the basal ganglia were no local sign, and only dominated the picture because of a lack of focal symptoms. Lewison and Alter (1923) described a case of glioma of the thalamus which did not show any focal symptoms. It was complicated by hæmorrhagic retinitis and optic neuritis which had led to amaurosis. The tumour protruded into the ventricle. Högner (1923) found disturbances of the pupillary reactions in 4 out of 20 thalamic tumours. He did not, however, mention the exact site of the growths. Seletzki (1927) described a tumour of the thalamus with no focal symptoms whatever. Alfred Meyer (1928) described a glioma of the thalamus which corresponded conspicuously with our "intrinsic" group. Both thalami were affected in their medial parts. The tumour expanded subependymally and in lateral direction. Meyer emphasized that at some levels it stopped short precisely at the lateral border of the thalamus. At posterior levels the field of Forel and the body of Luys were infiltrated. The tuber was free. The tumour extended backwards to the pineal gland. The main clinical symptoms were: fixed pupils, in the first stage pyramidal symptoms, later the tendon-jerks were diminished, there was drowsiness and a lack of attention and interest. The patient's intelligence, however, was not impaired. Because of radiological evidence of aortitis a diagnosis of lues cerebri was made.

Ody (1932) examined in Cushing's clinic 25 cases of tumours affecting the basal ganglia, and reached the conclusion that there were no focal symptoms characteristic of the basal ganglia. He emphasized particularly the complete absence of extrapyramidal motor signs such as athetosis, chorea, rigidity and tremor, a point which is confirmed in the present cases. The photograph of a thalamic glioma which he showed corresponded exactly in its mode of expansion with our " intrinsic " type of tumours.

Foerster and Gagel (1934) in describing a cyst of the 3rd ventricle discussed the relation between the diencephalon and mid-brain and emotional tone. According to them an antagonism exists between the two regions, for stimulation of the anterior part of the floor of the 3rd ventricle causes excitement and euphoria whilst destruction leads to apathy and somnolence. Reverse effects are produced by stimulation of the posterior part of the floor of the 3rd ventricle and the quadrigeminal plate.

More recently Riddoch (1936) described two cases of dementia which were caused by tumour of the 3rd ventricle. There was neither papillœdema nor increase of cerebrospinal fluid pressure, but hydrocephalus was severe and to this the dementia was attributed. In the case recorded by Mage and Scherer (1937) of a round-cell sarcoma which had a particular tendency to expansion round the 3rd ventricle, marked mental symptoms without local signs dominated the picture for a long time. The authors emphasize the same regarding the cases in previous literature (Fried, Környey, Scheinker).

In 1937 Baasch studied in Marburg's institute a glioma of the thalamus, aqueduct and pineal region. The patient had presented a picture of apathy with marked signs of internal hydrocephalus but no gross motor or sensory disturbance. The growth occupied the dorsal and medial parts of both thalami and was in its mode of expansion very similar to Meyer's case and to the present cases in Group II. The hypothalamus was unaffected. The tumour had a characteristic relation to the ependyma, and in its development it showed a very varying appearance at different levels. Baasch could distinguish five different types of growth each of which corresponded to a distinct type of Bailey and Cushing's classification. The largest part showed an appearance similar to that of diffuse gliomas of the pons (c.f. our Case 5). Because of its mode of expansion Baasch assumed that this glioma was of multicentric origin in the subependymal matrix. Hasenjäger (1938) examined in Spatz' laboratory 10 cases of glioma spreading along the ventricular walls. In one cross section of the brain she demonstrated two tumour masses, one in the thalamus and one in the lateral ventricle which, however, were parts of the same tumour. Besides this large mass she observed small neoplastic granulations in parts of the ventricle, and therefore she, too, came to the conclusion that these gliomas have a widespread " multicentric " origin.

Discussion of Results.

It is fully recognized that the essentially topographical nature of this investigation is by no means free from objection. Nevertheless the congruities between the cases themselves, and their many points of agreement with similar cases drawn from the literature, indicate the likelihood that a critical survey of symptoms in relation to the site of the tumour will give information of value.

In the accompanying table the 6 cases are grouped according as to whether the medial or lateral regions of the thalamus were primarily affected by tumour and it is at once apparent that this pathological division coincides with certain striking differences in the clinical picture.

In Group I (Cases 1 and 2) the tumours had destroyed a large part of the lateral and ventral regions of the thalamus and, clinically, gross sensory disturbances were present from an early stage of the disease. These were of the type commonly encountered in thalamic lesions ; the threshold for all sensory stimuli was raised but the impairment of postural and discriminatory sensibility was disproportionately great. The complete thalamic syndrome was present in only one case (Case 1) and here the initial symptoms were unpleasant sensations of cold about the right elbow and hand. Despite a marked hypalgesia on the right trunk and limbs pin-prick was peculiarly intolerable and this perverted response was widely diffused. The rarity with which the thalamic syndrome results from a neoplastic lesion is widely recognized. Possibly the time factor is of importance and it is perhaps significant that in Case 1 the duration of the disease was relatively long. In this group the significant pathological finding was the more or less complete destruction of the ventrolateral part of the thalamus and close histological examination made it plain that this region had been invaded early in the disease. In this respect these two cases offered a striking contrast to the four in Group II for here the more medial parts of the thalamus were most severely affected and it was evident that the tumour had spread into the lateral thalamic region at a comparatively late stage of the disease (fig. 7). Thus in Group II, whereas the ganglion cells in the region of the medial nuclei had entirely disappeared, the ganglion cells in the lateral and ventral nuclei were still well preserved and, indeed, in places the structure of these nuclei was entirely normal.

Clinically in none of these four cases were sensory disturbances among the initial symptoms and in two (Cases 5 and 6) they were completely absent, at any rate until the onset of the terminal coma. The absence or insignificance of objective sensory disturbances in those cases in which the ventrolateral thalamic areas were intact, or at least invaded very late in

TABLE OF CASES.

GROUP I.—VENTROLATERAL THALAMIC TYPE.

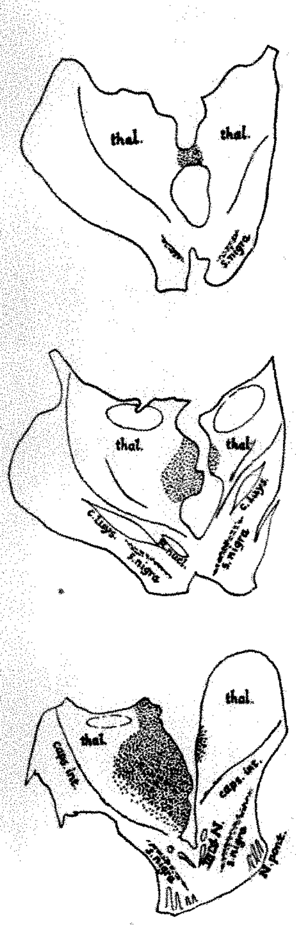
Case	Primary site of tumour	Initial symptoms	Motor signs	Sensory signs	Ocular signs	Mental deterioration	Evidence of hydrocephalus
1.—D. M. aged 50	Peduncular, capsulothalamic glioma	Paræsthesia	Hemiparesis (early), ataxia	Present at an early stage (thalamic syndrome)	Reflexiridoplegia at a late stage	Absent	Slight ventricular dilatation
2.—E. B. aged 43	Peduncular, capsulothalamic sarcoma	Monoplegia	Hemiplegia (early)	Early and severe sensory loss	Reflexiridoplegia at a late stage	Late in onset	Slight ventricular dilatation

GROUP II.—INTRATHALAMIC TYPE.

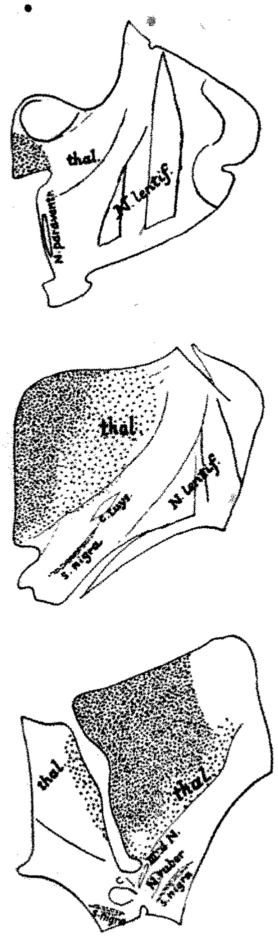
Case	Primary site of tumour	Initial symptoms	Motor signs	Sensory signs	Ocular signs	Mental deterioration	Evidence of hydrocephalus
3.—T. C. aged 64	Intrathalamic glioma	Mental deterioration (?)	Slight hemiparesis, gross ataxia	Difficult to assess but sensory loss certainly present	Ptosis (?)	Early and progressive	Considerable ventricular dilatation
4.—W. G. aged 67	Intrathalamic glioma	Mental deterioration	Slight hemiparesis and marked tremor	Definite sensory loss	Reflexiridoplegia probably early	Early and progressive	Ventricles of normal size, but c.s.f. pressure of 300 mm. water
5.—R. B. aged 63	Intrathalamic glioma	Mental deterioration	Absent until the terminal phase	Absent	Reflexiridoplegia and paralysis of upward gaze, probably very early	Early and progressive	Ventricles of normal size (c.s.f. pressure 140 mm. water)
6.—E. E. aged 43	Intrathalamic glioma	Mental deterioration. Internal ophthalmoplegia (?)	Absent throughout	Absent throughout	Reflexiridoplegia and paralysis of upward gaze	Early and progressive	Slight ventricular dilatation, c.s.f. pressure, 110 mm. water

the disease, stands in striking contrast to the gross sensory symptoms met with in those cases in which the tumour was primarily capsulo-thalamic.

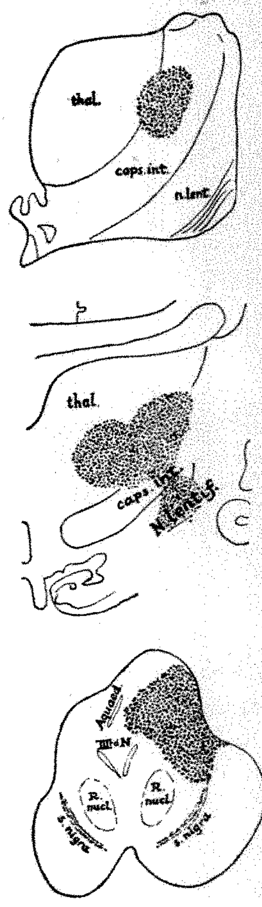
This contrast receives added interest from its bearing on the probable anatomical equivalent of the thalamic syndrome. Since the original description of this syndrome by Déjerine and Roussy (1906) it has been not uncommon to encounter relatively large thalamic lesions which, during life, gave no indication of their presence. The absence of sensory loss in such cases has always been puzzling for, until very recently, it was generally believed that the fillet system ended in relation with the whole of the thalamus and, therefore, it seemed inexplicable that destruction of any



Case 6·E·E·



Case 5·R·B·



Case 1·D·M·

considerable part of the thalamus should be compatible with a state of normal sensibility. As a matter of fact the resolution of this difficulty was given by Dejerine and Roussy (1906) and by Holmes and Head (1911) for in all their cases the lesions were confined to the ventral and posterior thalamic regions. Recent anatomical studies on the connection of the primate thalamus by Le Gros Clark (1932, 1935, 1938) and Earl Walker (1937) and the confirmatory experimental investigations of Dusser de Barenne and Sager (1937) have proved conclusively that the fillet system (medial lemniscus, spinothalamic tract, quinto-thalamic tract) terminates exclusively in the ventral thalamic nucleus and that the medial nucleus is not directly concerned with the mediation of impulses underlying sensation. If these observations are true for man they afford a satisfactory explanation for the integrity of sensation in those cases in which the ventrolateral part of the thalamus is either intact or invaded so late in the disease that the state of sensory functions cannot be ascertained.

The presence of a greater or less degree of hemiparesis in the cases in which the tumour had invaded the internal capsule and its absence in the two cases (Cases 5 and 6) in which the tumour had affected predominantly the medial part of the thalamus are entirely consonant with the view put forward by Dejerine and Roussy that hemiparesis is no part of the thalamic syndrome and, when present, is indicative of, and strictly proportionate to the extent to which the internal capsule is affected. It is interesting to note that a marked inco-ordination was present in three of the cases and, on the other hand, that there was no trace of inco-ordination in the two cases (5 and 6) in which the tumour was predominantly medial in position. The inco-ordination took the form of an action tremor and was entirely independent of visual control. In all three cases it appeared to be greater than could be accounted for by the weakness and sensory loss, and in Case 3 it was so gross that cerebellar disease was suspected. Ataxia has always been regarded as highly characteristic of the thalamic syndrome and it has often been reported in cases in which no other motor disturbances were present. The observations of Le Gros Clark and Earl Walker show that a large number of crossed fibres from the superior cerebellar peduncle passes to the region of the ventrolateral thalamic nuclei and from thence a further relay of fibres passes to the motor cortex. From this it would appear that the motor cortex receives impulses from the opposite dentate nucleus through the intermediary of the thalamus and interruption of this cerebello-frontal pathway is a possible explanation for the inco-ordination which may result from thalamic disease.

Disorders of ocular movement were present in five of the six cases here reported and, except in Case 1, they made their appearance at any early stage of the disease. Reflex iridoplegia was the commonest abnormality, being present in all five, but in three of the cases an associated paralysis of upward gaze was present at the time of admission to hospital. The frequency with which similar palsies have been reported in cases of thalamic tumour has already been mentioned and it is interesting to consider the possible mechanisms of their production. Actual invasion of the oculomotor nuclei was minimal except in Case 1 and it appears highly improbable that the very early onset of these ocular palsies was related to direct invasion of the nuclei, particularly as initially the palsies were strictly in terms of conjugate movement. A much more probable explanation is that there was interference with the supranuclear pathway. As Collier (1927) has pointed out there is good reason for believing that the paths for the light reflex and for upward and downward conjugate movement undergo a partial decussation in the posterior commissure, and, more recently, Magoun *et al.* (1936), by electrical stimulation in monkeys of the region of the posterior commissure and periaqueductial grey matter, have added experimental support to clinical observation. The tumours in the present series of cases showed a marked tendency to extend caudally towards the level of the posterior commissure and it is to this that the early ocular palsies are attributed. These ocular disturbances are of considerable practical importance for unless their possible significance is borne in mind, relatively benign conditions such as neurosyphilis or encephalitis may be diagnosed and the more grave lesion overlooked.

With the exception of Case 1 mental deterioration was prominent in the six cases studied and it becomes of some interest to inquire into the probable factors which determined its development. Attempts to relate mental functions to specific regions of the brain have seldom proved satisfactory and tumours in particular are generally unsuitable for such purposes. The concomitant hydrocephalus which is usually present and vascular disturbances and dislocation of cerebral tissue must often introduce factors the effects of which cannot be estimated. It is generally accepted that increasing apathy, confusion and finally coma are the common results of progressive hydrocephalus but, in regard to the mental defects consequent on destruction of brain tissue *per se*, Symonds (1931) has expressed an opinion, widely held, that mental deterioration is related to the total amount of white matter destroyed rather than to destruction of any particular region of the brain. For these reasons critical consideration of the mental state in Cases 1, 2, 3 and 4 is valueless. The tumours were large and had led to abnormally high intracranial pressure and ventricular dilatation.

Cases 5 and 6 were, however, much more interesting. In these two patients the tumours were relatively well circumscribed and there are indeed very good reasons for assuming that the lateral part of the thalamus was invaded at a late stage of the disease. The absence of detectable sensory disturbances in these two cases has already been discussed but the reason for the early and severe mental deterioration is by no means at once obvious. In neither case was the type of mental deterioration particularly unusual or suggestive. It was characterized by progressively increasing inattention, forgetfulness and disorientation. One of the patients (Case 5) rapidly developed a global dementia at a time when drowsiness was completely absent; the other (Case 6) did not become quite so grossly demented and here too there was no great evidence of abnormal drowsiness until within a few hours of death. In neither were signs of increased intracranial pressure at all marked, indeed apart from complaints of occasional headache in Case 3 they were entirely absent, and, finally, post-mortem examination disclosed a quite minor degree of ventricular dilatation. The frequency with which grave mental deterioration accompanies tumours in the region of the 3rd ventricle has already been alluded to but, whatever the cause of the dementia in many of these cases, neither ventricular dilatation nor massive destruction of white matter offers a reasonable explanation for its occurrence in Cases 5 and 6. It is therefore permissible to seek some more direct relationship between lesions of the medial part of the thalamus and the presence of a severe degree of dementia.

The observation of Le Gros Clark (1932), Le Gros Clark and Boggon (1935), and Earl Walker (1937, 1938) are pertinent in this connection for they have brought forward convincing evidence that the medial thalamic nucleus (n. dorso-medialis) projects exclusively to the granular frontal cortex and, furthermore, that this same nucleus is closely connected with the hypothalamus through the intermediary of the periventricular nuclei. It must be pointed out that in Cases 5 and 6 the tumour had extended across the massa intermedia into the opposite medial thalamic nucleus and it may be that this bilateral invasion of the medial thalamic nuclei was an important factor in determining the occurrence of dementia. This explanation is admittedly conjectural but it is at least worthy of consideration.

Having indicated the relationship that existed between the topography of these tumours and their symptomatology it seems necessary to outline the pathology of the intrinsic thalamic gliomas.

The isolation of well-defined types of tumour, based not so much on mere cytology but on their site of predilection and mode of expansion, has proved fruitful in the pathology of neoplasms in general and, more particularly, in relation to the pathology of meningiomas. The gliomas of macroglial origin appear to occur with almost equal frequency in all parts of the brain and to expand irregularly and this is probably one of the principal reasons why all classifications have been based solely on the morphology of the individual tumour cells. The cytology of the four gliomas in Group II may be dismissed with brief reference. All were astrocytomas in the broad sense of the term ; the tumour cells showed a varying degree of differentiation and malignancy both in different parts of the same tumour and in the several tumours themselves. In all four cases the tumours were intimately related to the lateral wall of the 3rd ventricle but in this region the cells were either differentiated astrocytes having a rich fibre network, as in adult subependymal astrocytes, or more primitive elongated cells with fewer processes or fibres. In neither case did they bear any resemblance to the primitive spongioblasts attached to the ependyma or to the cells of the primitive subependymal matrix. The appearance of the subependymal zones in these cases differed only in degree of development from the very small gliomas of the aqueduct which Shelden *et al.* (1930) have described. This similarity is remarkable because it indicates that the subependymal glia may actually be the point of origin of these gliomas. This conjecture is reinforced when it is remembered that the mode of expansion of the tumours such as occurred in Group II and in similar cases reported in the literature (A. Meyer, Baasch, Hasenjäger) showed, not only the peculiar attachment to the ventricular wall (which would cause no surprise in gliomas of the thalamus), but also expansion in the direction of the aqueduct, along the inferior horn of the lateral ventricle, and anterior to the vena terminalis towards the caudate nucleus. The most recent infiltrations were always found either in the lateral zones of the thalamus or in the white matter of the hemisphere. A most interesting common factor in all four cases was the complete integrity of the tuber. This does not, of course, imply that the hypothalamus as such is resistant to gliomatous growth. The invasion of this region is not uncommon in gliomas of other localizations (fornix, optic nerve) and, therefore, the integrity of the tuber in these cases of intrinsic thalamic glioma must be related to the nature of the growths themselves. Opalski (1934) in his study on the normal histology of the ventricular walls made an interesting observation in this connection when he pointed out that the subependymal glial layer is normally absent in the region of the tuber and the paraventricular nuclei. Elsewhere in the 3rd ventricle the subependymal glial layer is comparatively thin but it is noteworthy that in the region of the thalamus the fibrillary astrocytes normally extend into the area of the medial thalamic nuclei (Opalski). These observations all favour the hypothesis that the subependymal glial layer gives rise to the intrinsic gliomas of the thalamus. The term "intrinsic" in this respect, however, does not mean that these tumours originate exclusively in the thalamus. There was no sign that the areas of tumour in the roof of the mid-brain or neighbourhood of the lateral ventricle were of more recent origin. Hasenjäger's observations of small subependymal nodules of tumour growth in various places independent from one another and the diffuse subependymal gliomatosis in our Cases 5 and 6 favour the view that these tumours are of diffuse or "multicentric" subependymal origin. There is no resemblance between the cellular morphology of these tumours and the subependymal gliomas described by Roussy and Oberling (1931) as occurring in tuberous sclerosis.

Another important feature of the "intrinsic" thalamic gliomas was the tendency, in the early part of their life history, to be arrested at the margins of grey or white matter, and the same peculiar self-limitation was also apparent in the case reported by Alfred Meyer. This feature is, of course, not characteristic of the gliomas of the thalamus only ; it has been observed in gliomas elsewhere (Scherer, 1936) and in diffuse gliomatosis (Nevin, 1938). In the present cases, however, it is regarded as important because, together with the degree of destruction and degeneration, it indicated the mode of expansion. In all the four cases here reported and in similar cases reported in the literature, the tumour expanded from the neighbourhood of the ventricles in a lateral direction. From these several observations it appears justifiable and useful to regard these four cases of intrinsic thalamic glioma as representing a distinct and well-defined type of intracranial growth.

SUMMARY AND CONCLUSIONS.

Six cases of tumour affecting the thalamus (five gliomas and one sarcoma) are described clinically and anatomically and are compared with similar cases already reported.

Thalamic gliomas in a strict sense fall into a well-defined group. Histologically they appear to take origin from the subependymal glial layer and hence they have primary relation to the medial areas of the thalamus, to the caudate nucleus, roof of the mid-brain and to the walls of the lateral ventricles. They invade the brain in a lateral direction, and have little or no tendency to invade the region of the tuber. Clinically they are characterized by the early onset of mental deterioration, and early conjugate ocular palsies. Objective sensory disturbances are absent or appear only at a late stage of the disease. In the early stage of their development the presence of dementia and iridoplegia may readily suggest general paralysis.

In two cases the thalamus was invaded by tumour from its lateral and ventrolateral aspect. In these, gross sensory disturbances were present at an early stage of the disease.

The differing symptomatology of these two groups may be explained by the location and mode of extension of the tumours: in growths invading the thalamus from the ventrolateral aspect the secondary sensory neuron and its termination are destroyed first; in intrinsic thalamic gliomas which expand from the medial nuclei in a lateral direction the ventrolateral areas of the thalamus are invaded late and incompletely.

It is a pleasure to acknowledge our indebtedness to Dr. J. Godwin Greenfield for his interest and criticism, and for the use of his post-mortem records, and to the Honorary Physicians of the National Hospital who allowed us to make use of their cases and who placed their private notes at our disposal.

This work was carried out while Dr. Smyth held a Dickinson Research Scholarship and Dr. Stern the Kathleen Schlesinger Research Scholarship.

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CORTICAL DEAFNESS WITHOUT APHASIA.

BY W. E. LE GROS CLARK AND W. RITCHIE RUSSELL.

LESIONS of the upper part of one temporal lobe usually produce no disturbance of hearing in either ear. When, however, the auditory cortex of both cerebral hemispheres is diseased complete deafness may result. Cortical deafness, as this condition may be termed, is uncommon owing to the simple improbability of symmetrical lesions occurring in both temporal lobes. Henschen (1918) collected sixteen cases of cortical deafness which up to that date had been reported with *post mortem* examination. Since Henschen's valuable paper, Bramwell (1927) and Misch (1928) have each reported a further case. The case we are here presenting is unlike other recorded cases in that the lesions were both subcortical and were so limited that there was no associated aphasia.

Mrs. F., aged 44, was admitted, under Dr. Hewat's care, to the Edinburgh Royal Infirmary on April 9, 1937. The evening before admission, while sitting in a picture house, the patient had suddenly felt faint and vomited. At the same time she complained of pain in the right side of the head and of loss of power in the left arm and leg. She became dazed, but never unconscious. There had been no previous illnesses of note.

When examined on the day of admission, her face was flushed and she lay in a dazed condition with her eyes closed. She was able, however, to answer questions sensibly and indicated that she had pain in the right parietal region. Ophthalmoscopic examination revealed no abnormality in the appearance of the optic discs or the retinal vessels. The visual fields were normal. The pupils were equal and reacted normally. The ocular movements were full and normal. There was no sensory loss over the face. The facial movements were much less on the left side than on the right. Hearing was good in both ears. The palate moved in the midline, but the tongue was protruded slightly to the left. No movement of the left arm was possible and only very slight movement of the left leg could be made. Apart from some impairment of position sense in the left arm and left leg no sensory loss was detected. The tendon reflexes of the left arm and left leg were more active than on the right side. The left plantar response was extensor, while the right was flexor. The abdominal reflexes were all absent. There was retention of urine. The blood-pressure was 160/90 mm., and the heart was slightly enlarged to the left. The aortic second sound was accentuated. The urine contained no albumin or sugar. There was some vaginal discharge which was found to be free of gonococci. The urea concentration range was: maximum 1·8 mg. per cent.; minimum 0·2 mg. per cent. The blood urea was 27 mg. per cent. The blood Wassermann reaction was negative.

Progress.—Catheterization was necessary for six days after admission; thereafter control returned and the strength of the affected limbs improved greatly. She was able to walk a little when discharged on May 7, 1937, for further convalescence. Graduated exercises, massage and occupational therapy were continued, and the condition of the left arm and leg improved. In spite of a low protein diet and treatment with theominal and pacyl, the blood-pressure tended to rise, and on June 14, 1937, was 212/132.

Second stroke.—On June 22, 1937, the patient became dazed, incoherent and excited. The breathing became sterterous, but she was not unconscious and could, apparently, recognize people. There was incontinence of urine, but no paralysis was observed, though the patient seemed to be rather spastic. No detailed particulars of the examination on this day are available, but it was noticed that she had some difficulty in speaking for a few hours. The ability to speak and to read correctly quickly returned, but it was soon observed that the patient was quite deaf. She was, therefore, sent back to the Royal Infirmary on June 28, 1937.

When examined on the day of re-admission, the patient had a healthy and alert appearance. All efforts to make her hear were unsuccessful. She could, however, read and write without difficulty, and could speak clearly and correctly in response to written questions. She had no difficulty in carrying out written instructions. In response to written questions she stated that six days previously "I was right enough until after 10 o'clock at night when I began to feel queer and then I couldn't hear anything." She had been quite deaf ever since and had a sensation of loss of feeling in the whole body.

Examination elicited that there was now an extensor plantar response on both sides, whereas when previously in the ward this reflex was abnormal only on the left side. There were, however, no definite signs of weakness or loss of sensation in the right side of the body. The weakness of the left side had largely passed off, but there was still great exaggeration of the tendon reflexes on the left side. Those of the right side were brisker than when previously examined. Examination of the cranial nerves elicited no abnormality. No loss of sensation to pain could be detected.

The above observations allowed the diagnosis of cortical deafness due to bilateral lesions in the temporal lobes of the brain. Dr. I. Simson Hall kindly carried out the vestibular tests and reported as follows:—

The nasal septum is deviated slightly to the right, especially in its upper part; there are no abnormal secretions; the airway is not obstructed. Palatal movements and sensation in the palate are normal. The nasopharynx is healthy. The vocal cords move equally.

Vestibular functions.—There is slight initial spontaneous nystagmus to both sides but the movement is not preserved; there is no spontaneous past-pointing error.

Cold caloric test.—*Right ear*: Nystagmus in thirty-five seconds, strong reaction; deviation of the head is very marked; there is a normal past-pointing error.

Left ear: Nystagmus in thirty-six seconds. Past-pointing with the left hand is normal; with the right hand there is no error. Nystagmus is horizontal in character.

The patient gives no response with any cochlear function test; she appears to be completely deaf in both ears.

Progress.—Though the deafness remained complete, the general condition of the patient improved and she learned to lip-read a little. She was able to walk without much difficulty when she returned home on August 6, 1937.

The patient reported as an out-patient on three occasions during the five months which followed, the last occasion being on January 12, 1938. During this period her condition underwent little change. Her husband said she was easily startled, and there were a few attacks of violent excitement during which several people were required to restrain her movements. Her ability to read, write and speak correctly was demonstrated repeatedly. Her memory was good, both for recent and remote events. A name, address and flower were correctly repeated by the patient five minutes after reading them. The day was given correctly, and simple subtraction was done quite well. When asked if she had pain in her head, she said " no, it isn't a pain, it seems to be a heavy pressing feeling." She said she was unable to hear herself talking, and that there was no improvement in her hearing except that on two occasions she heard a bicycle bell and an alarm clock: she also thought she had once heard some loud singing.

The tendon reflexes remained brisker on the left side than on the right, and the left plantar reflex remained extensor in type. The right plantar response was indefinite. The patient could walk quite well with a stick, but complained that she could not feel the ground with her feet. She also remarked " I can't feel in my body." The exact nature of this sensory disturbance was not ascertained.

Arrangements were made for her re-admission to the ward for further study, but the excitement of leaving home seemed to bring on a pontine hæmorrhage from which she died a few hours after admission on January 22, 1938.

Post-mortem examination was carried out twelve hours after death by Dr. I. G. W. Hill who kindly supplied the following report:—

General Appearances:—The body was that of a well developed, well nourished female of middle age. Post-mortem lividity and rigidity present. Serous sacs, pericardial and peritoneal sacs healthy. Pleural sacs: The right showed extensive adhesions binding the right lung to the thoracic wall, which could be divided only with difficulty and were apparently of long standing. The left sac was healthy. Respiratory system: Larynx, trachea and bronchi contained a slight excess of muco-purulent secretion, and the mucosa of the trachea was moderately congested. Lungs of average shape and size, but heavy in consistence and dark red in colour. On section, they were seen to be the seat of marked congestion and œdema, particularly at their bases. Circulatory system: heart of average size and weighed 350 grm. The cavity of the right ventricle was somewhat dilated; that of the left ventricle was normal. There was slight thickening of the muscle of the left ventricle. The endocardium throughout was healthy. The muscle was of a rich brown colour. Coronary vessels healthy. Aorta free from gross atheromatous change.

Alimentary system: Œsophagus, stomach and intestines healthy. Liver of average size, shape and consistence: it was of a rich brown colour and presented no abnormality on section. Gall bladder: bile-ducts and pancreas healthy. Spleen considerably enlarged and weighed 280 grm. It was very soft and, on section, greyish red and diffluent. The appearances were those of reaction to an acute infection. Genito-urinary system: kidneys were somewhat reduced in size and weighed approximately 120 grm. each. They were smooth in outline and somewhat congested in appearance. On section, they showed no obvious pathological change. The capsules stripped readily, leaving smooth, congested surfaces. Microscopically, the kidneys showed no signs of chronic nephritis or of degeneration secondary to vascular disease. Suprarenals healthy. Uterus and appendages: the uterus was moderately enlarged, due to an increase in thickness of the wall. There was no sign of tumour formation, infection, or recent pregnancy. The ovaries were normal. The thyroid showed slight generalized enlargement and weighed 45 grm.

Brain (we are indebted to Dr. A. C. P. Campbell for the following report): "The calvarium was thick and heavy. The dura was normally adherent to it. The middle ear cavities were healthy. The brain showed considerable gyral flattening of both hemispheres, and marked cerebellar coning. The pons appeared symmetrically slightly enlarged, and on its left ventro-lateral aspect was a hæmorrhagic area where the underlying substance was softened. Apart from the gyral flattening there was no visible external abnormality of the cerebral hemispheres. The leptomeninges were healthy. The basal arteries were transparent and thin, and surprisingly free from atheroma. On section: In each hemisphere an irregular slit-shaped cyst was found deep to the insular cortex: that on the right was the larger; but on both sides the external capsule and claustrum were largely destroyed, with a varying amount of the putamen. On both sides the lesion extended backwards to the level of the pulvinar, and forwards almost to the stem of the sylvian fissure. On each side the acoustic radiation appeared completely transected by the lesion. On the right side the lesion encroached on the lateral surface of the internal capsule in its post-lenticular part. The cortex was not involved on either side. Both these cysts had an irregular tough brown-pigmented wall, and the immediately surrounding brain tissue was of spongy consistence: i.e. they were obviously old ischæmic necroses. It was not possible to say which was the older. A mass of fresh blood-clot was found infiltrating and replacing brain tissue in the left side of the pons and mid-brain, extending upwards into and largely destroying the left cerebral peduncle, the lower part of the left internal capsule and the adjacent ventral part of the left thalamus, including both left geniculate bodies; obviously an apoplectic hæmorrhage of very recent occurrence." The brain was sent to Oxford where the further examination was carried out by one of us (W. E. le G. C.).

Gross Examination of the Brain

Section of the brain revealed an extensive recent hæmorrhage in the pontine region of the hind-brain, the cause of the patient's death on January 22, 1938. The hæmorrhage was situated in the dorsal region of the left side of the pons, extending up into the centre of the left cerebellar hemisphere, into the tegmental region of the left side of the mid-brain, and also into the ventral half of the left thalamus involving here the ventral thalamic nucleus and the pulvinar. The 4th ventricle was filled with recent clot. The 3rd and lateral ventricles were normal except for a very moderate distension.

In the cerebral hemispheres, the sites of the lesions associated with the strokes which occurred on April 9 and June 22, 1937 (as the result of which cortical deafness supervened) are marked by a bilaterally symmetrical cavitation in the external capsule. The cavities are lined by a yellow membrane which was found histologically to contain abundant macrophages filled with granules of blood pigment. On each side the cavity corresponds almost exactly in its extent with the cortex of the insula (figs. 1 & 2). Rostrally (fig. 2*a*), it is limited to the white matter of the ventral half of the external capsule between the lentiform nucleus and the claustrum. In the middle of its extent (fig. 2*b*) it is broader, involving the greater part of the claustrum except for its dorsal extremity, and the ventro-lateral part of the putamen of the lentiform nucleus. At its caudal extremity (fig. 2*c*), which corresponds closely in level with the caudal limit of the insula, the lesion is again confined to the white

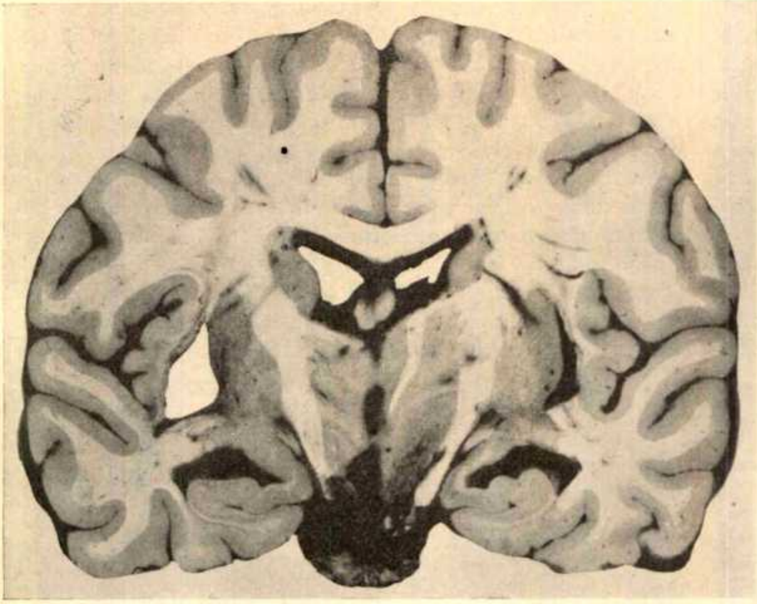

FIG. 1.—Transverse section of the fresh brain showing the bilateral lesions in the external capsule.

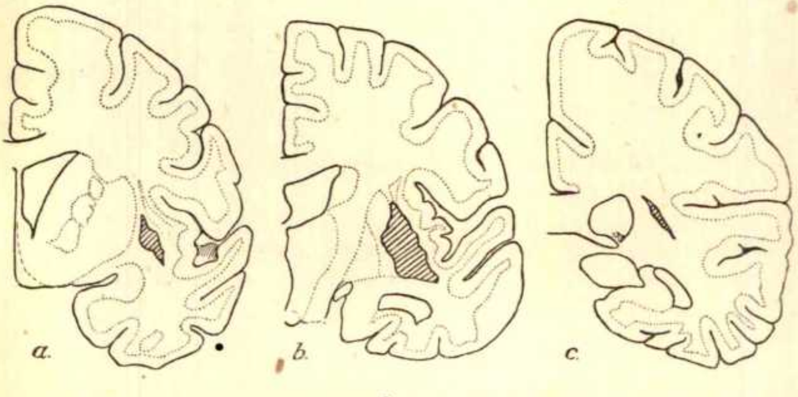

FIG. 2.—Tracings of transverse sections through the right cerebral hemisphere at the level of (*a*) the anterior extremity, (*b*) the middle, and (*c*) the posterior extremity of the lesion in the external capsule. Note that the lesion involves only the ventro-lateral portion of the putamen of the lentiform nucleus, while the globus pallidus remains intact. × ½.

matter. From the position of the lesion, as shown on macroscopical examination, it is clear that practically the whole of the insular cortex has been isolated from the region of the internal capsule by the interruption of projection fibres. It also appears that the fibres of the auditory radiations which pass to the upper surface of the middle third of the superior temporal gyrus have been interrupted. The experimental work of Poliak (1932) has shown that these radiations reach the cortex partly by coursing immediately ventral to the lentiform nucleus, and partly by penetrating its ventral part. Lastly, the dorsal margin of the lesion reaches a position where it is likely to have interrupted some of the projection fibres related to the ventral extremities of the central convolutions. It is clear that the lesions in the external capsules must have been the result of a bilateral thrombosis of the most laterally situated of the basal branches of the middle cerebral artery.

Histological examination.—Owing to the damage done to the thalamus on the left side of the brain by the hæmorrhage which occurred just before death, histological studies were confined to the right side. Sections through the site of the lesion were prepared by the Weigert-Pal method, and others were stained with toluidin blue. Serial transverse sections were also made through the caudal half of the thalamus and stained with toluidin blue in order to study the cellular degeneration related to the lesion in the external capsule.

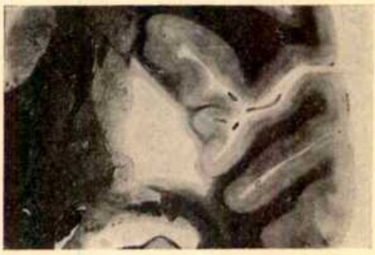

FIG. 3.—Transverse section through the middle of the lesion in the right cerebral hemisphere stained by the Weigert-Pal method. Natural size.

Weigert sections (fig. 3) confirm the inferences drawn from the macroscopic appearance of the lesion in regard to the involvement of projection fibre systems. The myelo-architecture of the insular and temporal cortex appears to be normal. The fact that the greater part of the claustrum has been involved by the lesion bears out the contention of Shellshear (1920) (as opposed to the statements of Duret and Beevor) that this element is partly vascularised by basal arteries and not entirely by deep cortical vessels which penetrate the island of Reil from the surface. On the other hand, the persistence of a subcortical layer of white matter beneath the island of Reil (capsula externa) is in accordance with the experimental demonstration that cortical vessels supply the subcortical medulla in so far as the latter is composed predominantly of fibres connecting with the corresponding area of the cortex (Sunderland, 1938).

While the Weigert sections give no indication of the extent of the cortex in the middle third of the superior temporal convolution whose fibres have been interrupted by the lesion, the toluidin blue material does provide evidence on this point, since the track of the degenerated fibres is marked out by a zone of gliosis (fig. 4*a*). From this it appears that only the fibres passing to the upper surface of the cortex have been involved. Since the lesion resulted in complete cortical deafness, it may be assumed therefore that the audito-sensory area is confined to the upper submerged surface of the middle third of the superior temporal convolution (i.e. the transverse gyri of Heschl). The auditory projection area of the medial geniculate body thus

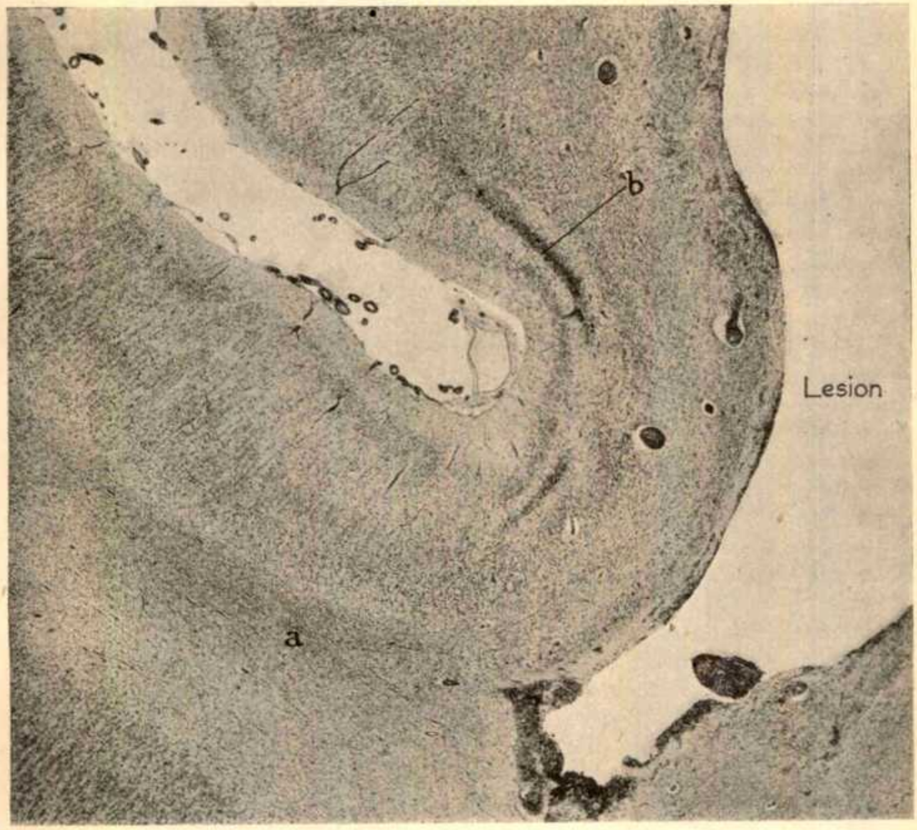

FIG. 4.—Transverse section through the lower margin of the lesion on the right side, stained with toluidin blue. Note the zone of gliosis (*a*) which marks the track of degenerated fibres of the auditory radiations passing to the upper surface of the superior temporal gyrus, and the small area of hæmorrhage (*b*) which affects the internal granular layer of cortex at the junction of the lower margin of the island of Reil with the superior temporal gyrus.

appears to be considerably more limited than some of the older neurologists supposed. Dejerine, for example, believed that the auditory radiations end in the whole of the superior temporal convolution, while, according to v. Monakow, they extend also to the second temporal convolution. However, recent experimental work on monkeys has demonstrated how small relatively the auditory area is in the Primate brain (Clark, 1936: Walker, 1937).

The toluidin blue sections show that the cyto-architecture of the insular and temporal cortex is quite normal with the exception only of a small area at the junction of the two. Here there is a curious vascular lesion limited to the internal granular layer of the cortex (fig. 4*b*). The granule cells have completely disappeared and are replaced by a proliferation of small blood-vessels and numerous macrophages filled with blood pigment. This can only be due to minute hæmorrhages involving the branches of the cortical vessels which supply the internal granular layer in this region, probably as a secondary result of the hæmorrhage in the external capsule. It is interesting to note, however, that the cortical lesion is confined to the one layer, for the cells of the supra- and infra-granular layers are normal. A marked congestion of all the cortical vessels in this zone, however, is evident.

The serial sections through the thalamus show some interesting features. The medial geniculate body is completely degenerated: its cells have all disappeared and are replaced by a conspicuous gliosis. Moreover, all the elements of the nucleus have been involved, including the large cells in the dorso-medial region which are sometimes included under the term nucleus supra-geniculatus. The lateral geniculate body appears to be normal ; if there is any cell atrophy in this element, it is too scattered and insignificant to be detected. Cell degeneration has also occurred in the small intergeniculate nucleus (between the medial and lateral geniculate bodies), in the most ventral portion of the pars externa and pars arcuata of the ventral nucleus, and, to a limited extent, in the lateral and central areas of the pulvinar. On the other hand, the cyto-architecture of the posterior projecting pole of the pulvinar is normal, and this is also the case with the lateral nucleus of the thalamus, the large medial (dorso-medial) nucleus, the parafascicular nucleus, and the greater part of the ventral nucleus.

From the point of view of the cortical connections of the thalamus, perhaps the most interesting observation is the almost total degeneration of the centre median nucleus. Its cells have completely disappeared except for an insignificant number at its medial extremity, and the space which it normally occupies is marked out by an area of gliosis sharply circumscribed above and laterally by normal cells of the medial and ventral nuclei and medially by the parafascicular nucleus. This effect of the lesion will be considered in another paper.

CONCLUSIONS.

The symmetrical vascular lesions in the external capsules have neatly isolated on either side the insular cortex, and the submerged cortex of the upper surface of the middle third of the superior temporal convolution. In addition a small proportion of the projection fibres connected with the lower extremities of the central convolutions was probably involved. In relation to these cortical lesions, an examination of the thalamus shows complete cell degeneration in the medial geniculate body, the intergeniculate nucleus, and the centre median nucleus. There is also a partial cell degeneration in the most ventral portion of the ventral nucleus and in the base of the pulvinar. The complete degeneration of the medial geniculate body is related to the cortical deafness which supervened when the vascular lesion in the external capsules occurred.

In addition to the acknowledgements already made, we are grateful to Dr. A. Fergus Hewat and to Dr. R. H. Thomson, Uphall, for kind permission to investigate the case under their care, and for their cordial assistance.

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CEREBRAL SUBCORTICAL MYELINOPATHY IN CARBON MONOXIDE POISONING.

BY Y. K. HSÜ
(Division of Neuropsychiatry, Department of Medicine, Peiping Union Medical College)
AND Y. L. CH'ENG
(National Central University, Nanking, China).

BILATERAL softening of the anterior part of the globus pallidus has been regarded as pathognomonic of carbon monoxide poisoning and used even for medicolegal purposes. The other acute and chronic changes in the brain described, though not so regular and typical, are thickening of the meninges, œdema, hyperæmia, miliary hæmorrhages, arteriosclerosis, endarteritis, thrombosis, embolism, softenings in the cerebral cortex, cornu Ammonis, zona reticularis of the substantia nigra and cerebellum, degenerative proliferative changes in the medulla, profuse glial proliferation and patches of demyelinization in the deeper cerebral white substance, cell destruction in the anterior horns of the spinal cord, and neuritis of the peripheral nerves. Compared with the extensive discussion of the pathology of the basal lesions, the diffuse reaction in the deeper white substance has been reported relatively seldom. Sayers and Davenport (1930) made a very thorough review of the literature up to 1930. Thereafter the scattered reports of various authors added few new ideas, but tended rather to favour multiple factors of the pathogenesis of this malady. In brief the various theories may be mentioned under the following categories: (1) direct action of the gas on the tissue (Gleister quoted by Mayers (1927), Dreser quoted by Meyer (1928), Mathews (1920), and Haldane (1927)); (2) a special physico-chemical affinity of certain parts of the brain (pallidum) for the gas (Vogt, C. and O. (1922); (3) anoxæmia (Strecker, Taft and Willey (1927), Henderson (1916), Haldane (1895), Beck (1936), Walters (1927), Haggard (1922), and Yant, Chornyak, Schrenk, Patt and Sayers (1934)); (4) organic changes of the blood-vessels (Sayers and Davenport (1930), and Hill and Semerak (1918)); (5) functional disturbances of the blood circulation (Meyer (1928), Klebs (1865), and Hiller (1924); (6) anatomical peculiarities and special arrangement of the blood supply to the basal ganglia (Kolisko (1893), and Poelchen (1888)); (7) a multiple factor (Stewart (1920), Gordon, Taylor and Margolies

(1932), Delafield and Prudden (1922), Grinker (1925), (1926), and (1934), and Hassin (1933)). Except for the last, practically none of these theories has been free from serious objection. The possibility of direct action of the gas on the tissue was excluded by the experiment of Haggard (1922). The theory of anoxæmia was supplemented by Mathews (1920), Lewin (quoted by Sayers and Davenport (1930)), Stadie and Martin (1925-26), Warburg (1926), Keilin (1928-29), Campbell (1929-30), and others, and doubted by Gippert (quoted by Stewart (1920)), and others. The theory of special pathoclisis can neither explain the frequent involvement of the neighbouring internal capsule nor that of the distant parts of the nervous system, nor the particular selection of the anterior portion of the pallidum, nor the similar symmetrical lesions of a totally different ætiology (Weimann (1926), and Rotter (1929)), nor the absence of permanent lesions in chronic carbon monoxide poisoning (Grinker (1925) and (1926)). Similarly the idea of local anatomical anomaly is inadequate, though it explains better the particular affection of the anterior portion of the pallidum. The organic changes of the blood-vessels cannot be demonstrated constantly. The theory of functional disturbances of the blood circulation seems very sound, but again it fails to answer the question of predilection of the lesions for the basal ganglia. Since none of the individual hypotheses is without defect, a multiple view-point would naturally arouse the sympathy of most advocates. At present the most acceptable view is that which invokes the physiological factors of anoxæmia, and of vascular disturbance, and the anatomical factor of peculiar blood supply.

In a small series of three cases with autopsies observed here, one showed typical bilateral hæmorrhagic softening in the globus pallidus with no significant changes in the white matter, and two presented diffuse changes in the deeper cerebral white substance, one of which was under the care of Dr. C. S. Yang, of Hsiang Ya Medical College, Hunan. Since two of three cases show a pathological picture which is not of the ordinary type, we feel it worth while to report them here.

Case 1.—Male, aged 40. Early in the morning, eight days before admission, the patient, a perfectly healthy man, was found lying unconscious in a cave just in front of a big stove. Consciousness returned twenty-four hours later and he resumed his usual activity, attending the stove for the next four days without any symptom. From the sixth day on he suddenly became excited and restless and showed much odd behaviour. His speech was slurred and his upper extremities tremulous. Very soon he became semiconscious and showed a generalized rigidity. He uttered no words, took no food or drink by himself, voided and defæcated on the bed without control. On admission he was found to be in a drowsy state with evidence of moderate dehydration. His eyes remained closed most of the time but could be opened in response to stimulus. He refused to reply to any question.

His neck was retracted. All extremities, including the hands, were held in flexion and were resistant to manipulation. Their rigidity was so great that they returned spontaneously to the original flexed position as soon as the counter-force in extension was released. To open his mouth was impossible. There was constant profuse perspiration over the face. The tendon reflexes were equally increased on both sides. The abdominal reflexes were not obtained. No clonus or Babinski sign could be demonstrated. The pupils were active to light. The fundi showed mild papillœdema. Hearing seemed not to be seriously affected, if at all. Sensibility to pin-prick was preserved throughout the whole body. Sudden jerky movements of the eyelids, nose and mouth were frequently noticed. Further neuropsychiatric examination could not be made. The chest and abdomen were essentially normal. The body temperature, pulse, respiration and blood-pressure were all within normal limits. Examination of the blood, urine, stool and cerebrospinal fluid gave negative information. The Wassermann reaction of both blood and cerebrospinal fluid was negative. Analysis of the blood for carbon monoxide by the gasometric method of Van Slyke and Neill revealed no detectable amount. During his stay in the hospital for forty-nine days he showed practically no change in his general condition. Hypodermic injections of atropine and electrolysis with magnesium chloride over the orbits produced no persistent influence upon the generalized rigidity. After discharge his condition became steadily worse and he died quietly about four months after the poisoning.

The body was immediately embalmed following death by injection of formalin into the femoral artery and the cisterna magna. Autopsy was done four months later.

The brain and the spinal cord were well fixed and normal in shape, size and consistency. The brain showed a diffuse shrinkage of the gyri. The meninges were thin and free from exudate and hæmorrhage. The pial and basal vessels showed no abnormality. Frontal sections revealed congestion of all the small blood-vessels. The caudal part of the thalamus on both sides and the interpeduncular region of the mesencephalon were of a slight darkish brown colour. The ventricles were not dilated. There was no hæmorrhage or thrombosis throughout. The spinal cord was essentially normal.

The histological changes were confined principally to the cerebral white matter, being pronounced locally at the internal capsule and the anterior commissure. A great abundance of "gemästete" glia and a moderate amount of "gitter" cells and hypertrophied microglia (red cells) were noticed throughout the deeper cerebral white matter with the exception of a narrow zone immediately below the cortical grey layers (U-fibres) (fig. 1). The distribution of the proliferative changes was diffuse and tended to be arranged in a certain pattern in relation to the engorged blood-vessels. The "gamästete" glia lay immediately next to the vessels; the "gitter" cells tended to be situated in an outer zone; and the rod cells were scattered at the periphery. Some of the blood-vessels showed deposition of greenish pigments on their walls.

Spielmeyer's myelin-sheath method revealed in the deeper white matter confluent patches of demyelinization with swelling of the sheaths and the formation of balls (fig. 2). The U-fibres were intact. The Scharlach R stain showed numerous lipoid globules arranged in a similar manner which appeared bright red at the centre and brownish yellow or orange at the periphery (fig. 3). However, a clear-cut relationship to the blood-vessels could not be demonstrated by either of these

PLATE XX.

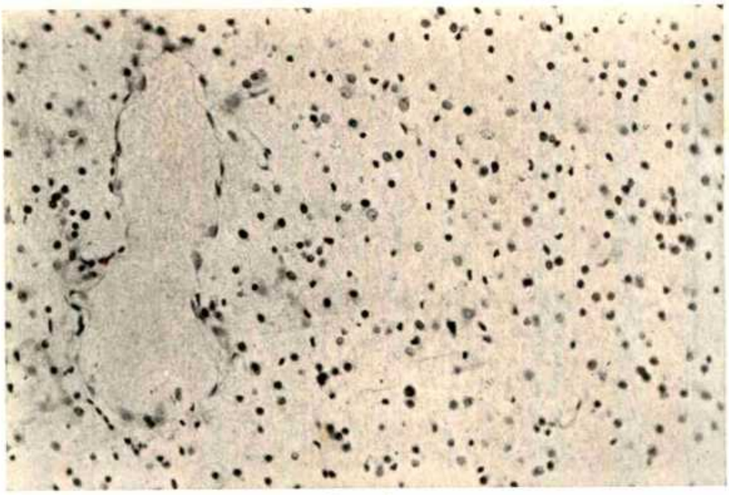

FIG. 1.

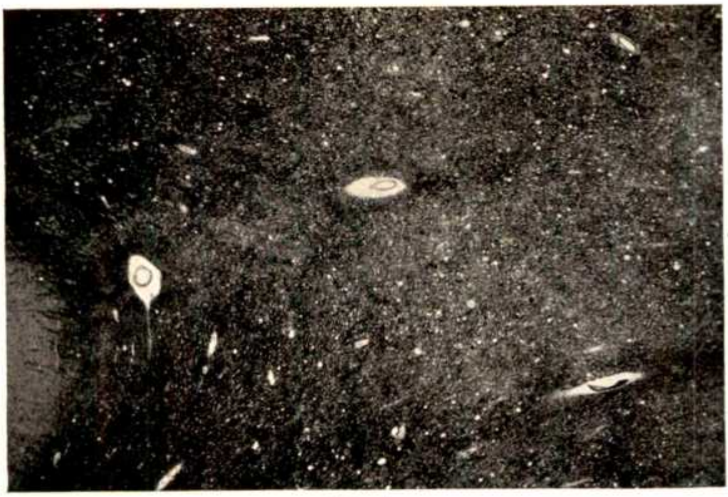

FIG. 2.

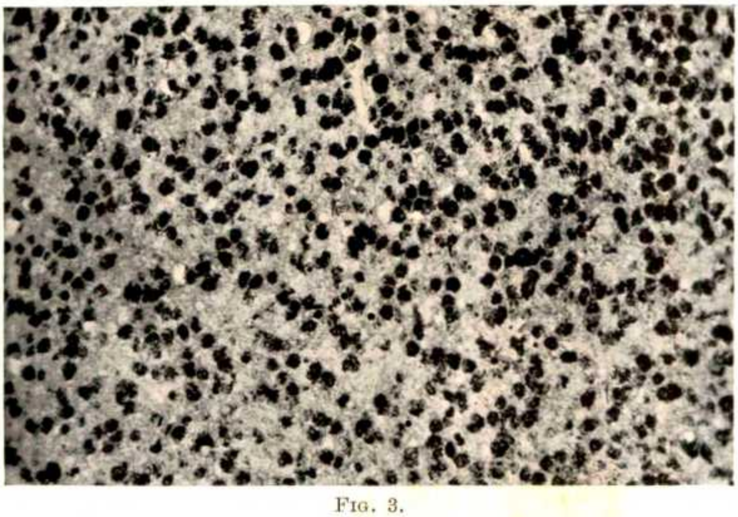

FIG. 3.

To illustrate article by Y. K. Hsü and Y. L. Ch'eng.

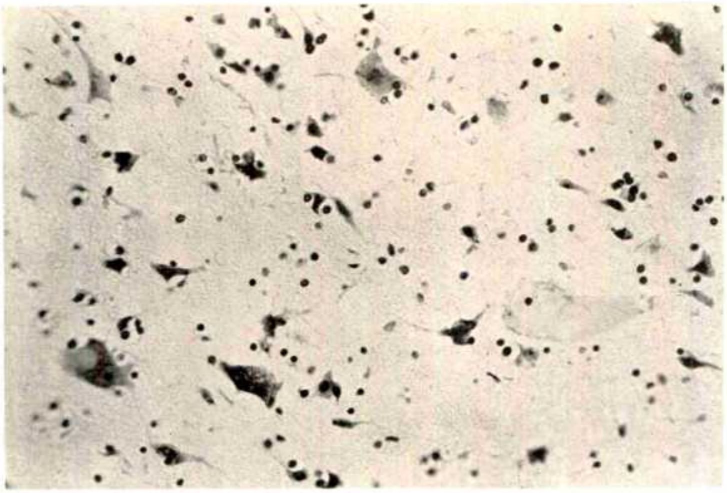

FIG. 4.

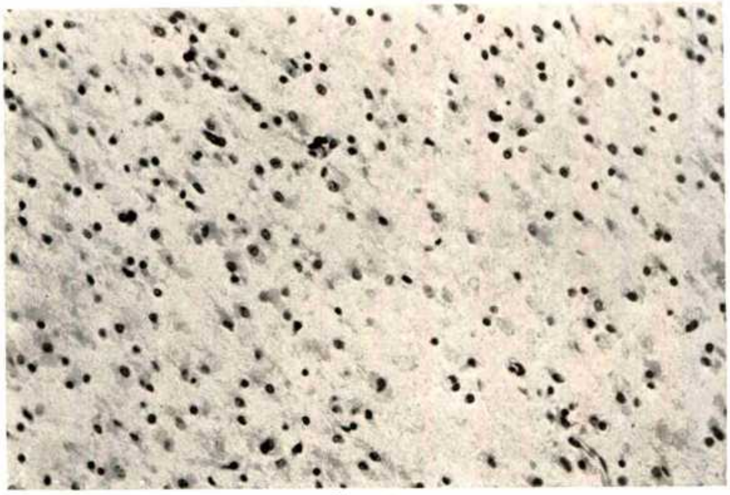

FIG. 5.

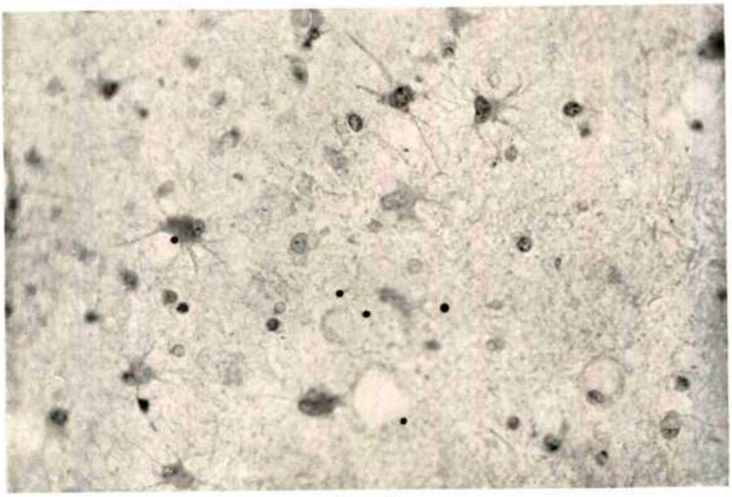

FIG. 6.

To illustrate article by Y. K. Hsü and Y. L. Ch'eng.

special stains. Many fibrous glia cells were shown by Holzer's method. The axis cylinders were diminished in number and slightly thickened with the occasional formation of balls.

Some of the ganglion cells in the third and fifth cortical layers appeared to be pale and swollen with the granular nucleus pushed to the periphery and the processes visible for a distance (fig. 4). The meninges were normal. There was no hæmorrhage or thrombosis.

Section through the left basal ganglia at the level of the anterior commissure showed disperson of "gitter" cells and "gamästete" glia in the corpus striatum, pallidum, internal and external capsules, and anterior commissure. These progressive changes were much more pronounced in the white substance than in the grey nuclei. The "gamästete" glia tended to be arranged around the blood-vessels, especially around those in the white matter near the border of the caudate nucleus. The special stains for myelin sheaths, fat, glial fibres and axis cylinders revealed a similar picture to that of the cerebral white substance. A tiny glial scar composed of "gitter" cells, fibroblasts and glial fibres was noticed at the inner border of the pallidum just adjacent to the internal capsule. No such lesion could be demonstrated in the corresponding right pallidum. The ganglia cells, except in the scar, were rather well preserved. The blood-vessels, especially in the caudate nucleus, showed slight lymphocytic infiltration of the adventitia.

The cerebellar white substance showed changes similar to those in the cerebrum, but they were much less marked than the latter.

The thalamus, mesencephalon, pons, medulla oblongata and spinal cord were essentially normal.

Case 2.—Male, aged 49. After sleeping one night in a closed room with a stove, the patient was discovered unconscious the next morning. Muscle-tone was increased, particularly in the right upper extremity. The condition gradually improved so that two days later he regained consciousness. Some râles were heard at the lung bases. While the general condition showed no change, there was definite evidence of extension of a pneumonic process in the left chest one week later. He suddenly appeared very ill and drowsy after another week and his temperature rose for the first time. Findings by this time suggested empyema of the left pleura and aspiration yielded thin pus from which the pneumococcus was grown. Then incontinence of urine and fæces set in and muscle-tone was further increased. Lumbar puncture yielded essentially normal cerebrospinal fluid. Following a short period of slight improvement the patient became much worse and died four weeks after the accident.

The post-mortem examination was limited to the brain. The brain appeared normal in shape, size and consistency. The meninges were slightly congested and showed a few small specks of thickening. The basal arteries showed no evidence of atheromatous changes. Frontal sections revealed slight congestion of the small blood-vessels, but were otherwise not remarkable. The globus pallidus on either side looked normal. The ventricles were not dilated. There was no gross hæmorrhage or thrombosis.

Throughout the entire cerebral cortex from the frontal to the occipital poles extensive changes were seen in the white matter. Only a narrow zone lying immediately underneath the cortical grey matter (U-fibres) appeared unaffected. In Nissl preparation there was a marked proliferation of the glial cells with numerous "gemästete" glia and "gitter" cells (fig. 5). These changes were especially pronounced around the blood-vessels and seemed to be arranged in a pattern similar to that in the first case. The blood-vessels were engorged and showed marked distension of their perivascular spaces, some of which were filled with pigment-loaded phagocytes. The vascular endothelium was, however, normal.

With Scharlach R stain, diffusely scattered fatty granule cells were seen with no special reference to the blood-vessels. With Spielmeyer's myelin sheath stain many of the "gitter" cells contained granules stained with hæmatoxylin and the picture was very uneven, with irregular thinning of the myelin sheaths. With Holzer's stain the fibrous astrocytes could be easily demonstrated (fig. 6).

Section of the anterior part of the basal ganglia revealed similar changes in the globus pallidus and all the white substance, including the internal and external capsules, fornix and anterior commisure. They were most marked in the internal capsule, less in the fornix and pallidum, and least in the external capsule and anterior commissure. Small fresh perivascular hæmorrhages were seen in the corpus striatum.

The cerebellum showed exactly the same change in the white matter as did the cerebrum.

A similar but less pronounced proliferation of glia cells was shown in the pes pedunculi, particularly the regions adjacent to the substantia nigra and the medial and lateral portions of the pes.

The meninges over the cerebral cortex were in places slightly thickened and infiltrated with a few large mononuclear cells. The pial vessels were normal. The small blood-vessels in the cortical grey layers were engorged, but otherwise not remarkable. The ganglion cells throughout the brain appear to be preserved. There was no evidence of inflammatory changes.

The pons and medulla oblongata showed no findings of significance.

Discussion.

In regard to the diffuse reaction in the deeper cerebral white substance caused by carbon monoxide poisoning, the observations of Hiller (1924), Grinker (1925, 1926 and 1934), Meyer (1928), Stewart (1920), Strecker, Taft, and Willey (1927), and Yant, Chornyak, Schrenk, Patty and Sayers (1934), deserve special consideration. It is, in fact, not so rare as reported and ought to be considered by no means less pathognomonic than bilateral softening of the globus pallidus. Ordinarily such a process is concomitant with the basal lesions and it is generally believed to be due to a severe alteration in myelin which was labelled by Grinker as myelinopathy. In our cases the lesions are principally the same as in theirs, but the absence of symmetrical softening in the pallidum is of extraordinary interest. This is in accord with Meyer's observations that the same independent change in the white matter may take place both in human cases and in animals. Obviously one should keep in mind the fact that affection of the pallidum is not necessary, in order not to miss recognition of the disease at the time of post-mortem examination.

As to the pathogenesis of the outstanding changes in the central nervous system the view of Grinker seemed to be the most adequate so far. He believed that carbon monoxide causes anoxæmia, and that vascular paralysis renders the anterior pallidum with its peculiar blood supply and the deeper white matter with its meagre capillary network relatively susceptible to destruction. But how does this explain those cases with independent changes, either in the basal ganglia, or in the white matter? How is this variation of distribution related to the duration of disease, the severity of poisoning, the personal susceptibility to the gas and the pre-existence of abnormalities in the brain ? To these questions no one can as yet formulate a definite answer. From our present observation we can postulate two possible mechanisms by which the degeneration of the white matter may occur. In case of an indirect effect of the poison through the disturbance of the circulation we should expect to find foci of necrosis in distinct relationship to certain vessels, or a more pronounced degree of degeneration in the district of a particular blood supply. In our preparations lesions of such a nature are absent. Then we have to think of a direct effect of the poison on the white substance in which case we should naturally expect to see a more or less immediate and diffuse reaction of the same age in the different parts of the nervous system. In contrast to Meyer's findings our cases show more of the nature of a direct toxic action to the white matter, either by the poison itself or by its anoxæmic effect. This being so, the metabolism of the nerve fibres or myelin sheaths is deranged and their nutrition becomes inadequate leading eventually to progressive degeneration of their structure.

In our first case the tiny glial scar in one pallidum certainly suggests the existence of a previous small necrosis. It is, however, only one-sided. The peculiar change in the ganglion cells is not unlike that described by Merritt and Springlova (1932), in Lissauer's dementia paralytica and by Williams (1935), in all kinds of degenerative changes in the subcortical white matter. Perhaps it did not result directly from the carbon monoxide poisoning, but it suggests an axonal reaction secondary to the lesions in the white matter. This is also the opinion of Williams. The infiltration of the adventitia of the vessels in the corpus striatum strongly suggests a symptomatic process.

In our second case, the significance of fresh diapedesis in the corpus striatum should not be over-emphasized. It is very unlikely that it is a sign of hæmorrhagic softening.

Clinically these two cases belong to the so-called relapsing type; that is, secondary changes appeared after recovery from the initial disturbances (Beck (1936), Borman (1926), Dancey and Reed (1936), and McConnell and Spiller (1912)). The interval of freedom is apparently due to the slow development of the pathological process in the brain which must reach a certain degree before producing symptoms. The picture of catatonia and Parkinsonism presented by our first case has been repeatedly described in carbon monoxide poisoning, and generally ascribed to a diffuse change in the white matter in respect of the psychic symptoms, and to the basal lesions in respect of the general rigidity (Strecker, Taft and Willey (1927), Meyer (1928), Stewart (1920), Gordon, Taylor and Margolies (1932), Grinker (1925, 1926 and 1934), and Dancey and Reed (1936)). From our observations it seems that both the neurological and the psychic symptoms can be accounted for by the severance of the connecting fibres between the cerebral cortex and the centres at a lower level. The absence of mental manifestations in our second case and the partial recovery from neuropsychiatric symptoms in Borman's (1926) suggest strongly that there is a lack of strict correlation between the appearance of mental disorder and the extent of anatomical lesions in the brain. The former seems to be related more closely to the individual constitution than to the duration of the disease and severity of the damage.

Since the fine lesions in carbon monoxide poisoning are often multiple and diffuse and may attack any portion of the nervous system, the symptoms may simulate many nervous and mental diseases (Beck (1936), Gordon, Taylor and Margolies (1932), Hassin (1933), Dancey and Reed (1936), and Wolff (1926-27)). Although pictures of catatonia and Parkinsonism are encountered more frequently than other syndromes, yet the finding of a diffuse reaction in the deeper white matter is of no less significance than that of basal lesions.

SUMMARY.

(1) Two "relapsing" cases of carbon monoxide poisoning with post-mortem examinations are reported.

(2) One patient presented symptoms of catatonia and Parkinsonism and died four months after the poisoning. The other developed early in the course bronchopneumonia and empyema, and died four weeks later.

(3) Both brains showed a more or less diffuse degeneration of the white matter with marked progressive changes of glia cells and patches of demyelinization. There was no bilateral softening of the globus pallidus.

(4) A direct influence of the poison, or its anoxæmic effect on the nervous tissue, is emphasized as an outstanding pathogenetic factor for our cases, in addition to the acceptance of Grinker's view.

(5) The discrepancy between the symptomatology and the extensiveness of the lesions is worthy of note.

(6) Attention is called to the significance of the changes in the deeper white matter in carbon monoxide poisoning.

We wish to express our great indebtedness to Professor W. Scholz for advice and encouragement in the preparation of this report and to Dr. C. S. Yang for allowing us to examine the brain of his patient.

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LEGENDS FOR PLATES.

Fig. 1.—*Case 1.* Frontal section showing proliferative changes of the glia cells in the white matter. Nissl stain × 220.

Fig. 2.—*Case 1.* Frontal section showing patches of demyelinization in the white matter. Spielmeyer's stain × 16.

Fig. 3.—*Case 1.* Frontal section showing numerous lipoid globules in the white matter. Scharlach red stain × 100.

Fig. 4.—*Case 1.* Motor cortex showing peculiar change of a large pyramidal cell. Nissl stain × 220.

Fig. 5.—*Case 2.* Occipital section showing proliferative changes of the glia cells in the white matter. Nissl stain × 220.

Fig. 6.—*Case 2.* Frontal section showing increase of fibrous astrocytes in the white matter. Holzer's stain × 295.

OLFACTORY ALLOÆSTHESIA.

BY JOHN D. SPILLANE.[1]

During the course of investigations of olfactory function in brain tumours, using the method recently described by Elsberg (1935), it was repeatedly observed that certain patients referred an odour injected into one nostril to that of the opposite side and failed to detect the odour on the side of injection. At first glance such a phenomenon might appear to be of little significance, merely suggesting a crossing of the stream of odour in the nasal passages or nasopharynx. However, special attention to the occurrence suggested that such was probably not the explanation. In this paper these observations are recorded and an explanation offered for the phenomenon.

The apparatus used and the principles on which tests of olfactory function were made have been fully described in previous papers (Elsberg, Brewer and Levy, 1935 and 1936) and only a short summary of the method will here be given.

Two tests are made: the blast injection and the stream injection tests. The former is made on the principle of the injection of a known volume of odour into one nostril during a period of voluntary apnœa. The apparatus consists of a test bottle of fixed size containing a known quantity of odorous substance (coffee or citral) and fixed with an inlet and an outlet tube. A known volume of air is injected into the bottle from a syringe and released into one nostril during a period of voluntary apnœa. The number of c.c. of odour that have to be released into one nostril in order that the odour be identified is termed the minimum identifiable odour (M.I.O.). The stream injection is used for the study of olfactory fatigue. A stream of air of known rate is passed from a tank of compressed air through the test bottle and thence to the nostril. Blast injections of the M.I.O. are then made into that nostril at thirty-second intervals, and the time that elapses before the odour is again identified is measured.

In twelve out of some ninety-two cases of suspected brain tumour examined by these methods, it has been observed that for a short period following the stream injection into one nostril, subsequent blast injections of the M.I.O. into that nostril were referred to the opposite side and not appreciated on the side of injection. In some cases this transference persisted for ten or twelve minutes following the stream injection. In each case it was observed that transference occurred in only one direction. For instance, in Case 1 (*see* table) blast injections into the right nostril following a stream injection into that nostril, were unhesitatingly identified as coming from the left nostril; but all odours injected into the left nostril, before and after a stream injection into that nostril, were readily localized to that side. The observations made on the twelve patients are summarized in what follows.

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[1] Commonwealth Fund Fellow at the Neurological Institute of New York City.

(1) In three of the twelve cases transference of odours was found on simple blast injections *before* the nostril on that side had been subjected to the stream injection.

(2) In a few instances, a doubtful case of transference before fatiguing with the unilateral stream injection, was converted into a well-marked phenomenon by administering the stream injection.

(3) In some instances the odour was correctly lateralized if, instead of blast injections of the M.I.O. being made, larger quantities were used. Thus, when a blast injection of the threshold stimulus, say of 8 c.c., was appreciated in the *other* nostril, an injection of 30 c.c. could be detected on the *correct* side.

(4) The phenomenon persisted for several minutes following the stream injection. In the majority of cases correct lateralization became re-established after six or ten minutes. (*See* table.)

(5) In eleven of the twelve cases the phenomenon was observed for both coffee and citral. In one it was present for coffee alone and was found to be inconstant for citral.

(6) Injections of air did not produce the phenomenon in these individuals. A blast of air, when appreciated, was never consistently referred to the opposite side.

(7) In ten of the twelve cases, the minimum identifiable odour and the duration of olfactory fatigue were within normal limits. The phenomenon of transference was the only abnormality.

(8) In a series of ninety-two individuals, normal or suffering from some form of nervous disease, only the twelve recorded instances were observed. The normal individual nearly always correctly lateralized the side of stimulation or else expressed doubt concerning the matter. He never consistently referred the stimulus to the opposite side while failing to identify it on the side of injection.

(9) In nine of the twelve instances of transference of the olfactory

stimulus, a cerebral tumour was found on the side on which the odour could not be detected. Thus, in a left-sided tumour such as Case 2, blast injections of the M.I.O. on the left side, following a stream injection on that side, were appreciated as originating in the right nostril, while no odour was detected in the left. A transference occurred from the diseased to the healthy side. In three instances, however, Cases 6, 9, and 10, the tumour was situated on the side to which the odour was incorrectly thought to have been applied. In these three cases transference was definite for both coffee and citral, and persisted for 12½ minutes, 8 minutes, and 13 minutes, respectively. Cases 9 and 10 were tumours of the acoustic nerve, arising in the cerebellopontine angle, and giving rise to hydrocephalus.

OLFACTORY STUDIES IN TWELVE BRAIN TUMOURS.

Case	Verified diagnosis	M.I.O.				Fatigue in mins.				Duration of transference		Direction of transference
		Coffee		Citral		Coffee		Citral				
		R.	L.	R.	L.	R.	L.	R.	L.	Coffee	Citral	
1	Rt. frontal astrocytoma	4	5	4	5	0	1·5	2	2	5 min.	5 min.	R. → L.
2	Lt. frontal meningioma	8	9	3	6	2	2	2	0	5 ,,	4 ,,	L. → R.
3	Lt. frontal glioblastoma	19	5	13	5	2	2	2	0	6 ,,	Nil	L. → R.
4	Lt. frontal astrocytoma	5	8	5	8	1	1	6	1	7 ,,	6 min.	L. → R.
5	Lt. frontal glioblastoma	6	7	8	8	2	2	1	4	7 ,,	8 ,,	L. → R.
6	Rt. frontal glioblastoma	6	8	4	6	2	3	2	0	12 ,,	11 ,,	L. → R.
7	Lt. parietal tuberculoma	8	7	6	4	1	1	1	0·5	4 ,,	3 ,,	L. → R.
8	Rt. fronto-temporo-parietal glioblastoma	12	8	11	7	0	0	0	0	9 ,,	10 ,,	R. → L.
9	Rt. fronto-temporal astrocytoma	11	8	18	6	3	0	6	0	8 ,,	8 ,,	L. → R.
10	Rt. acoustic neuroma	11	10	6	5	0	5	1	1	13 ,,	10 ,,	L. → R.
11	Lt. acoustic neuroma	22	8	10	7	1	2	1	5	10 ,,	10 ,,	L. → R.
12	Lt. cerebral neoplasm	13	8	17	17	8	6	5	5	8 ,,	8 ,,	L. → R.

Discussion.

The first possible explanation for the occurrence of the phenomenon is that some, or all, of the injected odour crosses to the other side in the nasal passages or nasopharynx. There are several reasons why this explanation is improbable.

(1) There was no history of injury to the nose and no deformity of the nasal passages in any of the recorded cases.

(2) If the odour crossed in the nasal passages or nasopharynx there would be no good reason why transference in any one individual always occurred in only one direction. If the odour crossed in the nasal passages, one would expect to see it occurring in both directions ; namely, from right to left *and* from left to right. Again, there would be no explanation why *all* the odour should cross and *none* be appreciated on the side of injection.

(3) In paragraph (3) above, it was shown that in some instances the odour was correctly lateralized if larger quantities were used instead of threshold amounts that were only appreciated in the opposite nostril. Such a condition could hardly arise if transference were taking place in the nasal passages.

(4) Two individuals with pituitary tumours (who did not show the transference phenomenon) with anosmia on one side and normal olfactory acuity on the other side, provided interesting experimental conditions. In one case the growth had been removed by transfrontal approach with injury to the olfactory nerve on that side, resulting in anosmia. In both these individuals, 30 c.c. of odour (approximately four times the amounts used in those individuals showing transference) released into the anosmic nostril from the test bottle were not appreciated either in that nostril or in the opposite healthy one. Similarly, sniffing strongly with the *anosmic* nostril did not at any time lead to an appreciation of the odour by the *sound* nostril. Therefore, if any degree of crossing of the odour occurred in the nasal passages under these conditions the quantity was insufficient for the stimulation of the healthy olfactory membrane and the identification of the odour. It may thus be concluded that under the conditions of the experiment much smaller quantities, such as were required for the demonstration of the transference in the twelve recorded cases, would have still less chance of stimulating the opposite healthy olfactory membrane.

(5) In order to determine whether, in normal individuals, any or all of the odour injected into one nostril may cross in the nasal passages to stimulate the opposite olfactory membrane, it was decided to produce a state of unilateral anosmia. This was obtained by spraying the olfactory membrane on one side with 1 per cent. novocain from an atomizer with a long slender tip. It was found that unilateral anosmia could readily be produced and that then blast injections and sniffing of an odour

on that side did not lead to an appreciation of the odour by the other side. Hence, it was concluded that blast injections of the odour did not cross in sufficient quantities in the nasal passages to result in an appreciation of the odour by the normal olfactory membrane.

(6) In olfactory studies by blast and stream injections the normal individual almost always correctly lateralizes the odour or else states that he cannot say on which side it is detected. He never consistently refers it to the opposite side while failing to detect it on the side of injection. The individuals showing transference, however, were never in doubt concerning the side which they thought had been stimulated. They all readily appreciated the stimulus but lateralized it incorrectly. No individual tested knew on which side the odour was injected, as the nosepiece fitted into both nostrils, although only one limb was patent. Repeated examination, suggestion and cross-examination failed to change them in their opinion ; indeed, in several instances, when the nosepiece was demonstrated to them, the odour continued to be appreciated on the wrong side even though the patient realized that the odour was injected into the opposite nostril.

We are thus forced to the conclusion that a condition, which may tentatively be termed olfactory alloæsthesia, exists in these individuals. A stimulus applied to one olfactory membrane is appreciated as if it arose from the other side of the nose. It may be advisable at this point in the discussion to consider briefly what has been described concerning alloæsthesia in general.

Sensory alloæsthesia.—Obersteiner (1881) was the first to give a clear description of this phenomenon of transference of a sensory stimulus from one side of the body to the other, which he termed " Allocheiria." He described its occurrence in four cases, two of tabes dorsalis, one of spinal cord injury and one of hysteria. He applied the term to a condition in which " though the sensibility is retained more or less completely, the patient is not clear, or is frequently, is not constantly, in error as to which side of the body has been touched. The stimulus is commonly referred to the corresponding point on the opposite limbs." Since that time numerous instances of alloæsthesia have been reported but little attention has been paid to its significance. It has been observed in hysteria (Obersteiner, 1881, Bosc, 1892, Verrier, 1898, Jones, 1907, &c.), in spinal cord injury (Obersteiner, 1881, Camp, 1908), in diseases of the spinal cord, notably in tabes dorsalis (Obersteiner, 1881, Déjerine, 1914, Hammond, 1883), following a head injury (Ferrier, 1882), in a brain tumour (Schilder, 1935), in hemiplegia (Kramer, 1915, Bosc, 1892), in bulbar apoplexy (Kramer, 1915), and in diphtheritic paralysis (Gay, 1893). In all the above instances a touch or prick stimulus applied to one side of the body was referred to a corresponding site on the other side; the transference in each case occurred in only one direction, viz. from the diseased to the healthy side of the body.

Brown-Séquard (1886) and Mott (1893) both observed it following hemisection of the spinal cord in monkeys. Dusser de Barenne produced local hyperexcitability of one side of a spinal cord segment of a dog by the application of strychnine and cut the sensory spinal pathways above the strychninized area on the same side. He then found that a stimulus applied to the other side was felt on the side of strychninization. It thus seems that hyperexcitability and simultaneous interruption of the sensory pathways on one side leads to irradiation of impulses to symmetrical parts.

Schilder (1935) records the case of a woman who, following a left-sided capsular and parietal vascular accident, showed a transfer of sensation from the left (healthy) side to the right (paralysed) side. There are only two other instances of such a transfer (Hammond, 1883, and Brown-Séquard, 1886). In all other cases the sensation was transferred from the diseased to the healthy side, as in nine of our twelve cases. Schilder (1935) has also described a case of brain tumour in which pin-prick on the left side of the body was appreciated on a corresponding point on the right side, although the patient would often scratch himself where he had been pricked. A pin-prick on the right side was localized with approximate accuracy. Pin-pricks on the face were always correctly lateralized. At autopsy a glioma was found to extend throughout the whole ventricular system involving both frontal lobes and the corpus callosum.

Auditory alloæsthesia.—There are three records under this title in the literature. The first, that of Gellé (1888) appears to be of doubtful nature. The second and third, published by Bonnier (1904) are described in detail. In both his cases a plug of wax in one meatus caused pain, deafness and unilateral forced movements, &c., which were referred to the opposite ear. Removal of the wax resulted in cessation of symptoms.

Visual alloæsthesia.—Two cases are recorded. Féré (1888) under the title of "Optic Allocheiria," described a female hysteric in whom the visual impression received by the right open eye was regularly referred to the left eye, the patient insisting that she received the impression with the left eye, which in fact was closed. Magnin (1888) also recorded a case of "Visual Allocheiria." An hysterical woman had total and complete left hemianæsthesia, which included the conjunctiva, cornea, auditory meatus and mucous membrane of mouth and pharynx. Smell, taste and hearing were abolished on the left side, and on this side there were also absolute achromatopsia and almost complete amaurosis. During hypnosis when both eyes were open, but their fields separated by a screen, a coloured object held in front of the left eye was recognized and the patient maintained that she saw the colour with the right eye.

Gustatory alloæsthesia.—Ferrier (1882) has recorded the case of a man who, following a blow on the head which rendered him unconscious for sixteen hours, developed complete alloæsthesia in both lower limbs and in the mucous membranes of mouth, tongue and nasal passages. Sensibility was intact throughout. A substance placed on one side of the tongue was tasted on the opposite side, although touch sensation itself was also transferred in the same direction. With the eyes bandaged, a touch stimulus was applied to one nostril and found to be regularly referred to the opposite nostril. Ferrier noted that as far as could be judged, the patient's sense of smell not being very acute, it was impossible to determine whether there was reversal of smell proper but only as regards the common sensibility of the nostril. The alloæsthesia persisted for five months.

We have been unable to find any reference to olfactory alloæsthesia in the literature.

Theory Propounded to Explain Alloæsthesia.

In 1883 Hammond put forward an hypothesis which has been considered an adequate explanation of alloæsthesia by the majority of writers on the subject. Following his study of the condition in a case of lateral sclerosis he concluded that "with a lesion in one posterior horn the sensation would be directed through the grey commissural fibres to the other posterior horn and would reach the cortical centre in the corresponding hemisphere, the sensation being then referred by this hemisphere to the wrong side of the body." Brown-Séquard in accepting this explanation stated that "Je ne crois pas qu'il y ait dans les faits d'allochirie rien de difficile à expliquer aujourd'hui que l'on sait que les deux moietiés de la moelle épinière, comme les deux moietiés de l'encéphale, ont de très nombreuses communications et que chacune de ces moietiés peut remplir le rôle de l'autre. On comprend donc aisément comment les impressions sensitives venues d'un côté du corps peuvent être percues comme si elles provenaient du côté opposé." It is difficult, however, to understand why, if alloæsthesia in spinal cord disease and injury is due to a unilateral lesion, it occurs so rarely. Bosc, in discussing his case of fatal cerebral hæmorrhage showing alloæsthesia, considered that impulses reaching the diseased cerebral hemisphere crossed through the corpus callosum to the opposite side and so were referred to the corresponding side of the body. This "blocking" hypothesis, whether applied to spinal or cerebral cases of alloæsthesia, received trenchant criticism from Jones (1907) who in turn considered the phenomenon to be an affection of "sidedness," due to psychical disaggregation. To the author, Hammond's theory does at least appear to offer an explanation which can account for the conditions described. A tumour in one cerebral hemisphere may prevent the correct perception and identification of an olfactory stimulus on that side, so that the impulse is in turn diverted to the opposite olfactory centres via the anterior and hippocampal commissures. It would then be referred to the nostril of that side. However, more accurate knowledge of the minute anatomy and the physiology of the rhinencephalon is required before the problem can be solved.

Summary.

(1) A condition has been described which has been tentatively termed olfactory alloæsthesia, in which a stimulus applied to one olfactory membrane is not appreciated on that side but is thought to arise in the opposite nostril.

(2) It is elicited in the majority of cases by first applying a prolonged stimulus to the olfactory membrane of that side, followed by injections at threshold level on the same side.

(3) In nine of the twelve recorded instances a cerebral tumour was found on the side from which the odours were transferred. A transference occurred from the diseased to the healthy side. In the three remaining cases a tumour existed on the opposite side. Transference occurred from the healthy to the diseased side.

(4) A brief discussion of alloæsthesia is presented and a hypothesis considered which may account for the phenomenon.

It is a pleasure to express my gratitude to Dr. Charles A. Elsberg for his encouragement and advice during the course of this investigation.

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DIFFERENCES BETWEEN EXPERIMENTAL RIGIDITIES IN CATS.

BY E. G. T. LIDDELL.
(Laboratory of Physiology, Oxford.)

AN earlier account described the effect of acute decerebration upon limb posture in cats some time after making experimental lesions of the spinal cord (Liddell, 1934, 1936). The lesion of the cord, which was on one side only, was originally and chiefly ventrolateral, but by spread of scar-tissue became also partly dorsolateral. It produced ipsilateral limb rigidity, i.e. hypertonia, presumably by " release " from some undefined control. Subsequent acute decerebration at intercollicular level wrought a remarkable alteration. The rigid limb became flaccid, the previously normal limb became rigid. Closer examination showed that the newly rigid limb was showing the classical decerebrate rigidity of Sherrington (1898), with " clasp-knife " collapse, whereas the now flaccid limb which had been rigid before decerebration, had been steadily resistant all the time that flexion was forced upon it, and there had been no clasp-knife collapse. Here, therefore, were two different types of rigidity producible at different times in the same preparation, and meriting further observation. As these results had not been due to the primary surgical lesion in the ventrolateral region but to the dorsally spreading scar, it was decided to make primary dorsolateral lesions, involving specially corticospinal pathways, and that has been done. Justified criticism is often levelled against spinal lesions in that they injure so much more than is intended and because " compensation " is so readily established. Compensation, however, at least in part, may be merely recovery from post-operative œdema which, in cats, is severe. As for the accurate determination of locality, it is well recognized that, even at best, histological methods can show reliably only dead tissue, as a rule, and not sick tissue which may subsequently recover.

METHODS.

Cats were used to the total of twenty-five, and allowing for the severity of the experimental procedures and the functional instability of preparations rostrally decerebrated, gave consistent results. The level of the cord-lesion was either that of the last rib, or in the lower part of the cervical region. The lesion was made with a Graefe knife, in the dorsolateral region of the cord (fig. 1), during nembutal anæsthesia and after aseptic exposure of the cord by partial laminectomy for a few millimetres. The lateral edge of the dorsal columns is easily defined and makes a reliable guide to the dorsolateral region. Silk sutures closed the muscle-layers and skin. For the next day or two, during recovery from the anæsthetic and the severest stage of cord œdema, no condition stands out definitely. On the whole, recovery from œdema is quicker, or its results in the lower limb less apparent, when the cord-lesion has been placed in the cervical region. The animal begins to walk freely about the fourth or fifth day, with normal gait. If recovery of walking ability is delayed, there may be noted, as on previous occasions, a distended bladder, out of control. Bladder control and ability to walk return together. A simple tension-spring dynamometer with a pan for pressing against the pad of the foot was held in the hand and used to flex the limb and measure the force needed. The flexing force must be imposed at the same rate at each trial, in order to assess accurately the plasticity of each limb.

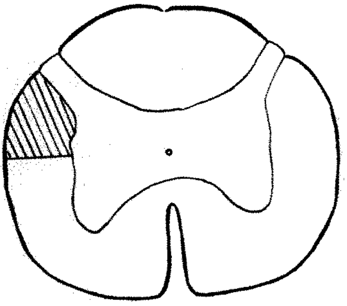

FIG. 1.—Diagram to show approximate extent of lesion in dorsolateral region of cord.

RESULTS.

Within two weeks of the operation, such activities as running, jumping and climbing are frequent, without any abnormality in the gait. When, however, the animal is nursed on one's knee, its trunk supported more or less vertically, its limbs protruded and partly hanging, the limb on the side of the cord lesion is evidently extended. (Upper limb changes are not considered here.) As previously mentioned (Liddell, 1936), this method of examination advocated by Langworthy (1928*a*) is essential for unmasking this kind of rigidity in cats, a finding which has since been confirmed by Bard and Rioch (1937). Thus when the cat is at rest, with its attention gently abstracted, the observer applies hand-pressure to its pad, or grips the ankle in order to flex the limb. Resistance of the muscles in the protruded limb, that is, on the side of the cord-lesion, is at once apparent. The protrusion, therefore, is not due to a paralytic hanging down, but is due to a contraction of those muscles which resist flexion. In an actively protruded limb, moreover, the ankle is usually well extended and not semi-flexed, as in a paralytic limb. With the dynamometer, a flexing force of 2 kg. or more may be registered as necessary for complete flexion, while the limb on the normal side needs only 1 kg. or less of pressure. Such readings are found in cats weighing 2 to 2·5 kg. If the animal is, at first, excited and tense, an increment of 1 kg. or more may be found equally on the two sides, but the difference between each total remains as before. After the first week, with the lessening of œdema in the cord, there may be some small addition, e.g. 0·3 to 0·5 kg. to both sides, but rather more on the normal side, as voluntary power returns fully. This is a more frequent occurrence when the lesion is at thoraco-lumbar rather than cervical level. There may, however, be an actual reduction in readings on the normal side, due, in reality, to a sharp voluntary withdrawal as soon as the pad is touched by the dynamometer pan. Subsidiary reactions in the rigid limb are (i) a flexion reflex from a pinch with a prolonged latent period, but often sharp enough when once elicited; (ii) a diminished ability voluntarily to flex the limb when struggling. The rigidity itself is a solid persisting resistance to the forced flexion, not altered in character but somewhat greater in amount when pressure is applied to the pad than when flexing force is applied to the malleoli by means of a loop of bandage. This slight difference might be expected from our knowledge of the positive Supporting Reaction (Magnus, 1926). The rigidity lasts to the very end of the flexion movement and there is no clasp-knife collapse as in decerebrate rigidity.

Rostral Decerebration.

That further interruption of the cerebrospinal pathways, other than that already achieved by the dorsolateral lesion, exercises no incremental effect upon the rigidity described, can be shown by acute rostral decerebration, under temporary ether anæsthesia and with temporary occlusion of the carotid arteries. Cortical tissue is completely removed and the central neuraxis is transected about the level of Winkler and Potter's section V (fig. 2). To examine such preparations, the method has to be modified in order to minimize the effects of their characteristic running movements, which, as is well known, begin some thirty to forty minutes after the transection and are generally held to mark the emergence of the preparation from "shock." The preparation is suspended from a high stand by two ligatures, one from the crown of the head, the other from the rump, so that the claws and feet have no place of purchase. If the preparation is laid on a table, or, if when suspended, the limbs are handled too much, severe spasms of running movements are frequent and the preparation becomes most unstable and inaccessible to examination. Then follow hyperpnœa and cardiac acceleration which lead to an early death from subtentorial hæmorrhage (Girndt, 1926). The risk of hæmorrhage appears at all times to be much reduced also by a diet of milk for some days preceding decerebration, although arterial pressure is raised thereby (Liddell and Carleton, 1937). Milk, therefore, is now always given to cats for some days before cerebral operations. Black cats, however, do seem specially liable to hæmorrhage.

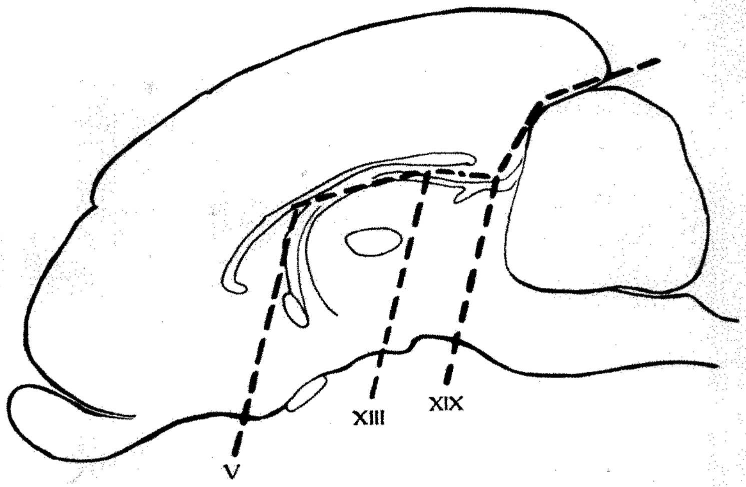

Fig. 2.—Diagram, after Winkler and Potter (1914), to show levels of decerebration. Cortical tissue is removed entirely and the brain-stem then transected at Winkler and Potter's levels. Level V is rostral to the greater part of the globus pallidus and to the crossing of the anterior commissure. Level XIII cuts the corpus callosum proximally from its splenium and, ventrally, is rostral to the corpora mammillaria. Level XIX passes between the anterior and posterior corpora quadrigemina.

Thus examined, it is evident within half an hour that the limb which before was the more rigid, is still the more rigid of the two. This may not appear until the carotid arteries, which were looped with loose ligatures before rostral decerebration, are released so as to give rostral tissues a better blood-supply. If the loops are tautened again, the limb differences may subside. This observation, not a constant one, suggests that rostral subcortical tissues play some part in the difference of limb rigidity (see also Liddell, 1938). In short, therefore, the limb rigidity which was previously established by the dorsolateral cord lesion has not been qualitatively altered by removal of rostral nerve tissues.

The preparation may then be subjected to a second and, this time, intercollicular transection of the brain-stem, as described below. Or it may be kept for six hours or more, during which time the neurological state remains unaltered, so long as the heart and respiration continues in activity.

The data from one such case will serve for illustration:—

Dorsolateral lesion of cord, left side, mid-cervical level. Wt. of cat 2·4 kg.

(*a*) 4 days later	left hind-limb	2·2 kg.,	right hind-limb	1·5 k.g.
(*b*) 7 ,, after (*a*) and 1 hr. after rostral decerebration	,,	2·3 ,,	,,	1·5 ,,
(*c*) 1 hr. after intercollicular decerebration	,,	1·1 ,,	,,	1·1 ,,

PRECOLLICULAR TRANSECTION.

If, instead of the rostral decerebration described above, the brain-stem is transected more caudally, e.g. Winkler and Potter's level XIII (1914) (fig. 2), there may be the same unaltered state as in rostral decerebrations. Or there may be a change, and the previously rigid limb becomes less rigid and approaches the condition of its fellow, which may be beginning to show some traces of decerebrate rigidity.

Data from such preparations are as follows:—

Dorsolateral lesion of cord, left side, mid-cervical level. Wt. of cat 2·6 kg.

(*a*) 12 days later,	left hind-limb	2·2 kg.,	right hind-limb	1·0 kg.
(*b*) 1½ hrs. after precollicular decerebration	,,	2·4 ,,	,,	1·8 ,,
(*c*) 1½ hrs. after intercollicular section, and 3½ hrs. after (*b*)	,,	2·5 ,,	,,	2·5 ,,

Same lesion as above. Wt. of cat 1·9 kg.

(*a*) 30 days later,	left hind-limb	1·5 kg.,	right hind-limb	0·5 kg.
(*b*) 1½ hrs. after precollicular decerebration,	,,	1·1 ,,	,,	1·1 ,,

INTERCOLLICULAR TRANSECTION.

This is Winkler and Potter's level XIX, for which the carotid arteries are permanently ligated. Whether the preparation is fresh or has been previously decerebrated more rostrally, either the limbs become equally rigid or the previously rigid limb may be slightly less flaccid than its fellow, as indicated by the examples quoted. In the latter event, the smaller degree of rigidity on the operated side can be safely ascribed to the observation by Sherrington (1898) that dorsolateral lesions, especially at the thoracic level, may reduce decerebrate rigidity, though not so fully as do ventrolateral lesions. The former result, i.e. equal rigidity, is a common one.

Discussion.

Experiments to investigate posture modify or impair it in different ways. Hence comes in the cat a solid persisting rigidity in extensors, after cortical lesions or dorsolateral spinal lesions; a "clasp-knife" rigidity with exaggerated postural precedence in extensors, as in decerebrate rigidity, or a co-contraction with diminished but still overpowering precedence for extensors, as in the positive Supporting Reaction. By what nerve-paths or the balance of action of what mechanisms these modifications or reductions of normal posture are brought about, remain still to seek.

These present results accord with the earlier experiments, described in the introduction to this paper. In the present series, the original lesion is dorsolateral and its effect circumscribed by avoidance of secondary effects from scar through a shorter duration of experiment. In any preparation decerebrated at intercollicular level, a ventrolateral lesion is a profound reducer of rigidity. In the undecerebrate animal, such a lesion does not reduce and may even enhance the rigidity from a dorsolateral lesion. Thus it is only when interruptions are both dorso- and ventrolateral that rigidity is severe enough to appear in the cat's gait as spasticity (Liddell, 1936).

The postural over-action released here in the first stage of the experiment by the dorsolateral spinal lesion alone, although almost equal to the body-weight of the animal, is overshadowed in the gait, which, as Graham Brown has emphasized, is basically a spinal rhythm. (Graham Brown, 1914, *a*, *b*.) Only when the animal is quietly nursed on the operator's lap is the rigidity revealed.

Subsequent acute removal, under ether anæsthesia, of cortical tissue ("rostral decerebration"), leaving only basal tissue, does not alter in quality or quantity the pre-existing postural state. But as the decerebrating level becomes more caudal and approaches intercollicular level, the pre-existing solid rigidity tends to be replaced by "clasp-knife" rigidity. On the side ipsilateral to the cord lesion, this is of full or slightly diminished amount, for reasons quoted (Sherrington, 1898). On the other, normal, side there is also decerebrate rigidity, here of full amount. The gradual development of rigidity of this type as intercollicular level is approached is one of its characteristics (Langworthy, 1928 *b*). That after rostral decerebration, there is no alteration of cord-lesion rigidity may be merely that corticospinal paths, already severed by the spinal lesion, are now severed again, at the higher level. Since the experiment is acute, the functional significance of the level cannot be accurately defined, but the functional level is not far below the anatomical level of decerebration (Bazett and Penfield, 1922).

At present, however, the main finding is that in one and the same preparation of cat, two expressions of exaggerated posture can be distinguished. In monkeys, Fulton and his colleagues have shown that decerebrate rigidity is to be distinguished from decorticate rigidity (Fulton, 1938). In the former, the fore-limbs are " thrust backward in rigid extension with pronation," in the latter, they assume "a strongly-flexed hemiplegic posture." Thus according to the status of the animal, different lesions bring to light, by release, different expressions of *functio laesa* in the complex nervous machinery which integrates muscle posture.

SUMMARY.

(1) In cats, dorsolateral lesions of the spinal cord on one side are followed by rigidity in the ipsilateral limb. The rigidity is distinct from decerebrate rigidity. Both kinds of rigidity can be demonstrated at different times in one experimental preparation.

(2) The rigidity from the cord lesions steadily resists forced flexion and has no " clasp-knife " collapse. Although the rigidity may resist a flexing force equal to the animal's body-weight, it is not apparent in the gait.

(3) When the animal is decerebrated at intercollicular level, classical decerebrate rigidity develops in the fellow limb, and has " clasp-knife " collapse. The previously rigid limb, ipsilateral to the cord-lesion, alters the quality of its resistance and may now also show a " clasp-knife " collapse. It may, however, show rather less rigidity because the original dorsolateral lesion may have severed some paths which play a small part in sustaining decerebrate rigidity, when this is made to appear by the intercollicular section.

(4) When the level of decerebration is precollicular or at levels so rostral that the decerebration is rather a " decortication," and when classical decerebrate rigidity cannot be expected to develop, the rigidity obtaining from the spinal lesion is often not altered either qualitatively or quantitatively. The pattern of release, therefore, remains unchanged by these forward decerebrations.

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OBSERVATIONS ON NERVOUS RELEASE.

By E. G. T. LIDDELL.
(*Laboratory of Physiology, Oxford.*)

SHOCK or diaschizis in the nervous system is a well-recognized entity. It is an abeyance or reduction of reflex function at neurone-to-neurone junctions, following the interruption of some large path which normally supplies background excitation to the neurone junctions and keeps the neurones in a state of low activity (Sherrington, 1899, von Monakow, 1914, Liddell, 1934). Similar to the conception of shock as a withdrawal of subliminal excitation, is the withdrawal in "release" of low-grade or subliminal inhibition. It is probable that in release there is destroyed a path which normally inhibits in part or whole some integrated group of neurones, so that, after release, the group shows an aspect of activity which previously it did not show. A familiar example of release is the exaggerated postural activity following intercollicular transection of the brain-stem—"decerebrate rigidity" (Sherrington, 1898). Although release, as a rule, is believed often to need some hours or days to declare itself, decerebrate rigidity appears immediately, unless the anæsthetic is very profound indeed.

Now in shock, as Sherrington (1906) showed for spinal pathways, a second interruption of the excitatory path does not seriously deepen the degree of shock produced by the first interruption. In release, therefore, if it is a comparable phenomenon, the second interruption of an inhibitory path should not, or need not, alter or increase the degree of release from the first interruption.

The experiments now described have for their starting point some observations by Sherrington (1899), which were later pursued by McCouch (1924), and by Fulton and McCouch (1937). Sherrington (1899) wrote: "The cat from which the Rolandic area of the cortex has been removed, so as to ablate the whole of the limb centres, if some weeks later decerebrate rigidity be induced in its limbs, yields the rigidity without perceptible difference between the sides, both right and left." "In the monkey, similarly prepared, a great difference between the limbs on the sides is apparent. The rigidity on the side crossed to the cerebral lesion is very much less than on the homonymous side."

RIGIDITY AFTER CORTICAL LESIONS (MOTOR AREA) AND THE EFFECT OF SUBSEQUENT DECEREBRATION.

Methods.—Six cats were used in this series. Under nembutal anæsthesia, and with full asepsis, the cruciate sulcus was exposed frontally, by traversing the frontal sinus. The sinus was swabbed with 1 : 1000 acriflavine and gave no septic trouble. The cortical lesion was made on the lips of the cruciate sulcus, by electro-cautery, about 3 mm. square, in order to minimize subsequent paralysis. Preliminary experiments without the cautery had shown that for obtaining a small release of posture, it was not necessary to follow meticulously the accurate localizations of Langworthy (1928). Subcuticular sutures of silk closed the scalp.

Twenty-four hours later, when the effects of anæsthesia had passed, a release of limb posture was found in the contralateral limb, but was not at all evident in the gait. (Only hind-limbs were examined regularly.) In order to reveal the release of posture, the animal must be nursed on one's knee, as described in the preceding paper. An early sign of release is the absence or lessening of the flexor reflex in the affected limb, or a prolongation of the latent period of the reflex. In general, the animal's condition follows closely that after dorsolateral cord lesions, as described in the previous paper (Liddell, 1938). The affected limb is protruded and more rigid than its fellow. Dynamometer readings were taken, as previously described.

Results.—The history of one preparation (Animal No. 1 of Table) may be given in some detail. Its lesion covered the outer extremity of the anterior sigmoid gyrus, area C of Langworthy (1928) (fig. 1). The cerebral lesion was on the left hemisphere, so that the rigidity developed in the right limbs. The hind-limb showed solidly resistant rigidity, without clasp-knife collapse. After forced flexion, the limb extended again readily, i.e. the flexors were not seriously implicated. The cat weighed 2·2 kg.

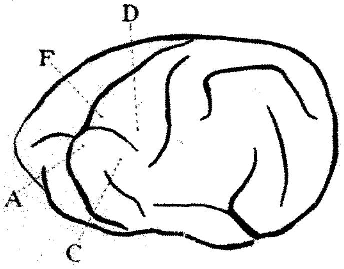

Diagram of cerebral hemisphere of cat, after Langworthy. The lettering of the anterior and posterior sigmoid gyri follows that author.

1	day	after	cortical	lesion, left	hind-limb	resistance	0·2	kg.,	right	1·4 kg.
4	,,	,,	,,	,,	,,		0·0	,,	,,	2·0 ,,
11	,,	,,	,,	,,	,,		0·1	,,	,,	1·5 ,,
20	,,	,,	,,	,,	,,		0·4	,,	,,	2·0 ,,
24	,,	,,	,,	,,	,,		0·2	,,	,,	1·6 ,,

On the twenty-fourth day, after a rostral decerebration at Winkler and Potter's level V (see fig. 2, previous paper), under ether anæsthesia, the preparation was suspended for examination by strings from the head and rump. The following readings were obtained:—

20	minutes later,	left hind-limb	resistance	1·2	kg.,	right hind-limb	1·2	kg.
30	,,	,,	,,	1·2	,,	,,	1·4	,,
40	,,	,,	,,	0·6	,,	,,	1·4	,,
50	,,	,,	,,	0·4	,,	,,	1·0	,,
60	,,	,,	,,	0·6	,,	,,	1·2	,,
135	,,	,,	,,	1·0	,,	,,	1·5	,,

Although these readings fluctuate, the extreme instability of the preparation has to be kept in mind (Girndt, 1926), as well as the gradual passing-off of anæsthesia and "shock." It is evident that the left hind-limb has an accession of postural release from a previous average resistance of 0·8 kg., to a present average resistance of 0·8 kg., while the right limb, previously rigid from the cortical lesion, has suffered some decrease, from 1·7 kg. average to 1·3 kg. average. But the feature to be noted at this stage is that the previously rigid limb is still the more rigid.

150 minutes after transection at level V, the transection was made intercollicular (ether anæsthesia):—

10	minutes later,	left hind-limb	resistance	0·4	kg.,	right hind-limb	1·2	kg.
15	,,	,,	,,	0·5	,,	,,	1·6	,,
30	,,	,,	,,	0·8	,,	,,	1·8	,,

Thus, even after intercollicular transection, the previously more rigid limb remains the more rigid. Animal 5, decerebrated at intercollicular level without previous forward decerebration, showed still a difference like animal No. 1, although the cortical lesion had not produced a very marked difference in the otherwise intact animal. Animals 2 and 3 gave trace of previous release after rostral decerebration, though not after intercollicular transection. From these preparations, it is evident that rigidity from decerebration, whether intercollicular or more rostral, need not be by itself a full release, because the release in the previously rigid limb persists and adds itself to the newly established rigidity.

One animal, No. 4, was similarly prepared but was decerebrated at intercollicular level without previous rostral decerebration. It gave results in accordance with those of Sherrington (1899).

Animal 6 shows the difference in resistance between a preparation functionally decerebrated at a low level by looping of the carotids, and the same preparation functionally thalamic, with carotids free. This preparation, so far as the general results of decerebration are concerned, accords with Sherrington's preparations.

DISCUSSION.

These experiments, though small in number, are significant if related to the results in the previous paper (Liddell, 1938). Here a lesion, established in the motor cortex some three weeks previously, may (but need not) continue to document its release of postural mechanism, even after it has been ablated from the animal, along with all other cortical tissue, in the rostral decerebration. The lesion, though ablated, may assist, and increase the release achieved by acute ablation, which, by itself, is shown in the fellow-limb. In other words, later acute release from decerebration may have added to it the earlier chronic release from the cortical lesion.

SUMMARY.

The release of postural activity in limb musculature of cats which is wrought by chronic lesions of the motor cortex may remain after the cerebral hemispheres have been removed acutely either by rostral, intermediate or intercollicular decerebration, and the limb which was the more rigid before decerebration, remains the more rigid after it. In continuing its effect, therefore, after acute decerebration, this release shows itself to be a phenomenon with properties comparable to those of its physiological enantiomorph, nervous shock.

TABLE.

No. of animal	Wt. kg.	Duration of observation period. Days	Lesion	Average limb readings in kg.		Readings after rostral decerebration		Time after rostral decerebration	Readings after intercollicular decerebration		Time after intercollicular decerebration
				L. hind limb	R. hind limb	Left	Right		Left	Right	
1	2·2	24	Area C (fig. 1) Left side	0·18	1·7	0·6	1·2	1 hr.	0·8	1·8	½ hr.
2	2·5	54	C + D Left	0·15	1·8	1·2	2·0	1 ,,	0·4	0·4	½ ,,
3	2·6	55	D Right	1·6	1·0	2·0	0·73	2 ,,	1·0	1·0	1½ ,,
4	2·3	23	C Right	1·5	0·4	—	—	—	0·7	0·7	1 ,,
5	3·0	22	F Left	0·8	1·1	—	—	—	1·3	1·8	3 hrs.
6	2·5	27	A Right	1·5	0·2	1·0 0·7	1·2 0·7	Carotids free Carotids looped			

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A DEFORMITY OF THE HIND-BRAIN ASSOCIATED WITH INTERNAL HYDROCEPHALUS. ITS RELATION TO THE ARNOLD-CHIARI MALFORMATION.[1]

BY ADAMS A. McCONNELL AND H. LEE PARKER.

On five occasions suboccipital exploration for cerebellar tumour has revealed, instead of a tumour, a deformity of the lower part of the medulla oblongata and a prolongation of the cerebellar tonsils into the spinal canal. The appearance of the parts exposed by operation, and in three of the cases studied post mortem, suggests a relationship to the Arnold-Chiari malformation described in cases of spina bifida.

Case 1.—Male, aged 18. Headache, vomiting, failing vision. Papillœdema. Involvement of 11th cranial nerve on left side and of 9th and 12th on the right. Suboccipital exploration, pressure cone and tumour of medulla. Post-mortem examination, deformity of medulla.

H. C. was admitted to the Richmond Hospital, Dublin, on May 15, 1935, on account of headache and vomiting.

Five months before admission, he began to suffer from attacks of throbbing pain in the frontal and occipital regions and in the back of the neck. These attacks increased steadily in number and severity and later were accompanied by vomiting.

On May 14 paroxysmal headache and incessant vomiting reduced the patient to a stuporous condition, in which condition he arrived in hospital.

Examination.—The patient was a sturdy, well-built youth. He was drowsy, stupid and non-coöperative. Temperature 102° F., pulse 100. There were clinical signs of consolidation of the lower lobe of the left lung. Radiological examination confirmed the clinical signs and also revealed slight but typical lesions of early tuberculosis. Papillœdema of 5 D was present in each eye with numerous retinal hæmorrhages and exudate. The right pupil reacted very sluggishly to light, the left was practically inactive. Hearing seemed to be diminished on the right side. There was definite weakness of the right side of the soft palate and weakness and atrophy of the right side of the tongue. On the left side of the body the trapezius muscle was very weak. All tendon reflexes were increased but the plantar responses were flexor.

The pneumonic process cleared up completely in ten days but by this time the papillœdema had increased to 7 D in the right eye and 6 D in the left. There was marked ataxia in the upper and lower extremities on the left side. The right side was normal. At no time was he able to get up and walk.

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[1] An extension of a paper read at the Annual Meeting of the American Neurological Association, Atlantic City, N.J., June, 1937.

Radiological examination of his skull showed digitations all over the vault and some rarefaction of the dorsum sellæ.

A diagnosis was made of tumour in the region of the foramen magnum because of evidence of damage to the lower cranial nerves on both sides and because of the increase of intracranial pressure.

May 30, 1935.—Operation: Avertin and local anæsthesia. The usual exposure of the cerebellum was made. There was a considerable amount of tension in the posterior fossa which was somewhat relieved by tapping a lateral ventricle. The arches of the first and second vertebræ were removed before the dura was opened.

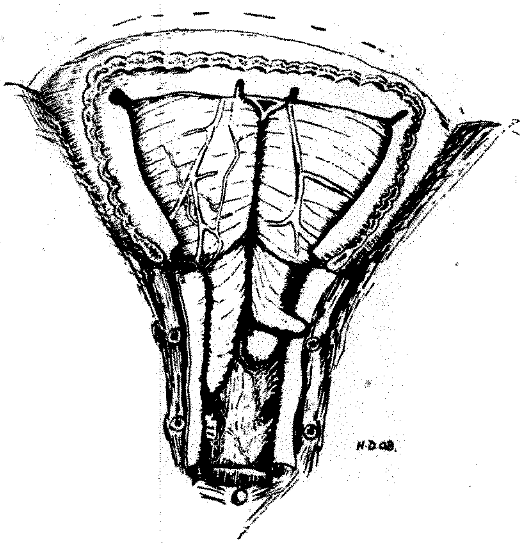

FIG. 1 (*Case 1*).—Diagrammatic sketch of the cerebello-medullary region at the time of operation. The prolongation of the cerebellar tissue below the foramen magnum, the upward course of the cervical nerve roots, and the nodule on the medulla can be seen.

The cerebellar hemispheres bulged through the opening in the dura and a very tense and unusually long pressure cone was present. Separation of the tonsils below the foramen magnum was accompanied by a free flow of cerebrospinal fluid and the tension subsided completely. Further separation disclosed the lower third of the 4th ventricle. When the right side of the pressure cone was displaced, a protuberance was noted on the dorsum of the medulla. It occupied the right half of the closed part of the medulla, and was situated caudal to the foramen magnum. It seemed to rise sharply from the dorsal surface of the cord and to merge gradually into the medulla. The first cervical nerves arose below the level of this nodule and inclined obliquely upwards to their exit from the canal (fig. 1).

The diagnosis at the time was tumour of the medulla oblongata and since a free communication had been established between the 4th ventricle and the subarachnoid space, the operation was concluded.

The patient recovered consciousness shortly after the operation and seemed to be doing well for the next forty-eight hours. He then became suddenly comatose. Ventricular puncture was done immediately. There was no tension in the ventricle and death occurred soon afterwards.

Permission was given for partial necropsy only. The brain was removed entire, but the spinal cord was cut at its junction with the medulla. There was a definite internal hydrocephalus which affected all the ventricles.

Macroscopic examination of the brain and the meninges revealed no other pathological changes. Sections of the brain-stem showed no tumour either grossly or in serial sections examined under the microscope.

Case 2.—Male, aged 10. Headache, hiccough, staggering gait. No papillœdema. Internal hydrocephalus. Operation, deformity of cerebellum and medulla. Post-mortem examination.

Q. L. was admitted to the Richmond Hospital, Dublin, on March 29, 1936. His chief complaints were headache and a staggering gait.

Twelve months before admission he had had a very severe attack of bronchopneumonia which lasted for some weeks. He was delirious part of the time. During his convalescence headaches began. They were chiefly situated in the occipital region, more frequently present in the morning upon awakening, and they lasted for a few hours. Vomiting was not common but there were very frequent attacks of hiccough. The staggering gait was noticed soon after the onset of the headaches and both symptoms were becoming increasingly severe.

The child was well-nourished, was confined to bed, and had a marked squint due to paralysis of the left external rectus muscle. The fundi were normal. There was marked nystagmus on lateral gaze, which was present also on looking upward, though to a less degree. His head was normal in size and shape. His speech was scanning in character and there was definite inco-ordination in the upper extremities on performing the usual tests. His tendon reflexes were all exaggerated and the plantar responses were both extensor. The gait was spastic and ataxic, but the patient could make progress unaided.

The differential diagnosis seemed to lie between an arachnoiditis of the cisterna magna secondary to bronchopneumonia and a medulloblastoma of the vermis cerebelli.

On April 2, 1936, the lateral ventricles were tapped and found to be dilated. Thorotrast was injected and rœntgen studies were made. Every portion of the ventricular system was visualized and found to be evenly dilated. No thorotrast, however, had passed into the cisterna magna.

The usual cerebellar exposure was made. The dura was under considerable tension which was relieved at once by puncture of the posterior horn of the lateral ventricle. When the dura mater was opened widely it was found that the cisterna magna was of moderate size and that there was no thickening or opacity of the arachnoid membrane. Both cerebellar hemispheres appeared normal except for the presence of a pressure cone. In order to expose the cone completely the posterior arches of the atlas and axis were removed. On the right side the cone extended downwards to the level of the axis, and on the left side to the upper edge of the lamina of the 3rd cervical vertebra. Each side of the cone was thin and flat with hard and ivory-white tips quite different in appearance from the usual pressure cone. When the cone was displaced a nodule was seen on the dorsum of the medulla (fig. 2). Further separation opened the 4th ventricle and there was a free flow of fluid mixed with thorotrast.

The calamus scriptorius was at the level of the foramen magnum. The nodule appeared to be on the right side of the closed part of the medulla and below the foramen magnum. The lower part bulged sharply backwards from the brain stem but its upper part faded away gradually. It was about half a centimetre long and a little less than that in width and just barely crossed the middle line. The first and second cervical nerves emerged from the cord below the nodule and inclined upwards. The wound was closed in the usual way. The patient's general condition was good at the end of the operation, but later there was some cyanosis although the breathing was not markedly embarrassed. Death occurred suddenly at 10 p.m. that night.

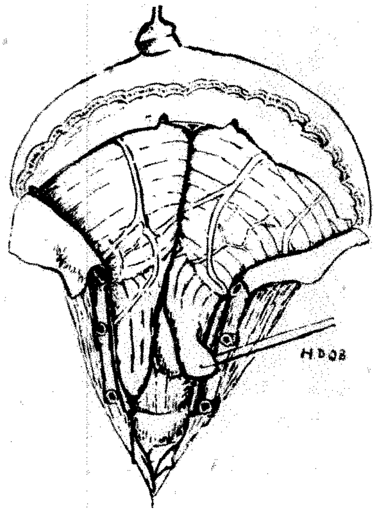

FIG. 2 (*Case* 2).—Sketch showing prolongation of the cerebellum into the spinal canal. The hardened tips of the cerebellar tissue have been separated diagrammatically to show the nodule on the dorsum of the medulla.

Necropsy was performed on the day of death, and as in Case 1 was limited to an examination of the brain and upper portion of the spinal cord. The operative findings were confirmed. Sections of the whole brain and of the brain stem in particular failed to disclose any neoplastic or other cause for the symptoms other than the deformity of medulla and cerebellum.

Case 3.—Female, aged 32. Buzzing noise in head, vomiting. Later headache and staggering gait. Late onset of slight papillœdema. Marked internal hydrocephalus without tension. Operation, deformity of cerebellum and nodule on medulla. Recovery.

T. L. was admitted to the Richmond Hospital, Dublin, on February 10, 1936. Her chief complaints were a buzzing noise in her head and vomiting.

In June, 1935, when on holiday, she suddenly became conscious of a buzzing noise in her head.

A month later she began to vomit, chiefly in the morning and without nausea. At first the vomiting occurred about twice a week but later became a daily affair. In August, 1935, headache accompanied the vomiting. The headache was occipito-cervical in location and as time went on became increasingly severe. In December, 1935, she became very unsteady on her feet. Flexion of the head on the chest seemed to relieve the staggering.

At the beginning of her stay in hospital, the outstanding feature was the early morning vomiting. Later on, the headaches became a more prominent feature. The buzzing noise continued without intermission. The eye grounds on repeated examination were normal up to May 10, 1936, when very slight papillœdema appeared. Radiological examination of her skull showed nothing abnormal. Her blood-pressure was 100 millimetres systolic and 60 diastolic.

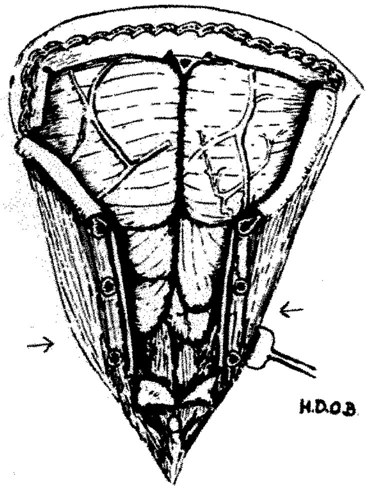

FIG. 3 (*Case 3*).—Diagrammatic sketch of conditions found on removal of the occipital bone atlas and axis.

The first impression of her case was that she was suffering from Addison's disease. Blood urea 20 mg. per cent. Blood sugar 115 mg. per cent. Plasma chloride 592 mg. per cent. Serum calcium 10·1 mg. per cent. B.M.R. – 10.

Frequent neurological examinations showed nothing more than an ataxia of gait commensurate with her profound weakness and her bed-ridden state. On walking she held her head stiffly and tilted to the left. There was no nystagmus.

May 18, 1936.—Ventriculography: When the needle was passed into the ventricle no fluid escaped through it, but 90 c.cm. of fluid were gradually aspirated and replaced by air. The pictures showed a marked internal hydrocephalus involving the 3rd and 4th ventricles. The diagnosis of adhesions obstructing the outflow of cerebrospinal fluid from the 4th ventricle was made. The cerebrospinal fluid was normal in every respect.

Immediately after the ventriculography the posterior fossa was explored in the usual manner under local anæsthesia. There was no tension when the dura was exposed, and on opening it, bubbles of air were seen in the cisterna magna. The cerebellar hemispheres appeared normal, except for a very marked prolongation of the tonsils which simulated a pressure cone. The right tonsil reached a point below the arch of the atlas, whilst the left extended to that of the axis. The right tonsil was rather bulky as was the upper part of the left, but the lower third of the latter was thin, feathery and rather yellow. Appearing under the right tonsil was a whitish nodule rising abruptly from the brain-stem and occupying apparently all the right side of the medulla (fig. 3). Its widest part was below the level of the arch of the atlas. The first cervical nerve emerged from the cord just below the nodule and ascended obliquely upwards to its exit from the spinal canal. There seemed to be abundance of room for the structures passing through the foramen magnum. The presence of air bubbles in the cisterna magna indicated that there was no obstruction to the exit of cerebrospinal fluid from the 4th ventricle. Accordingly nothing more was done and the wound was closed.

The patient had a slow convalescence. At intervals of four or five days she complained of severe frontal headaches associated with vomiting. These attacks were always relieved by the withdrawal of 10 c.cm. of fluid from a lateral ventricle, but it is interesting to note that the fluid was never under tension and had to be aspirated. Similar relief was obtained later during her convalescence by the administration of magnesium sulphate by mouth. She returned to her work as a waitress in September, 1936.

For the next seven months she frequently wakened in the morning with a feeling of nausea which continued until she " retched " up with difficulty about a teaspoonful of yellow or green fluid.

The patient was last seen in June, 1938, more than two years after the operation. She was cheerful, comfortably fat and " able for anything." She stated that she occasionally " brought up a mouthful of bitter stuff " in the morning and that she was quite unable to eat anything until the afternoon. The cerebellar decompression was flat. There was no trace of staggering in her gait and no abnormal neurological signs were found.

Comment.—The chief differences between this case and the two preceding were the more insidious onset, the relatively few signs of involvement of the central nervous system, and the successful outcome. The surgical findings were essentially the same and the appearance at operation suggested that the prolongation of the cerebellar tonsils into the spinal canal had been present for a considerable period and was not a recent occurrence. A similar nodule or knuckle was present on the dorsum of the medulla. It is noteworthy that there were no signs of increased intracranial pressure either on examination of the eye grounds, at the operation, or on tapping the ventricles after operation. The cause of the patient's symptoms must remain unexplained. The result was excellent and it is possible that her recovery was due to the fact that no attempt was made to liberate the cerebellar tonsils.

Case 4.—Female, aged 26. Headache and failing vision. Papillœdema. Pulmonary tuberculosis. Cerebellar exploration, deformity of medulla. Recovery.

B. J. was admitted to the Richmond Hospital, Dublin, on March 4, 1938, on account of headache and failing vision.

One month before admission she noticed that she had some difficulty in reading the paper and in sewing. About the same time she began to wake about 7.30 a.m. with a slight headache which grew worse until she had dinner at 1 p.m. when it gradually subsided but never completely disappeared. "Headache powders" often gave partial relief. The headache was always frontal in position and dull in character. Occasionally the patient felt dizzy but she never staggered nor fell. Family history good.

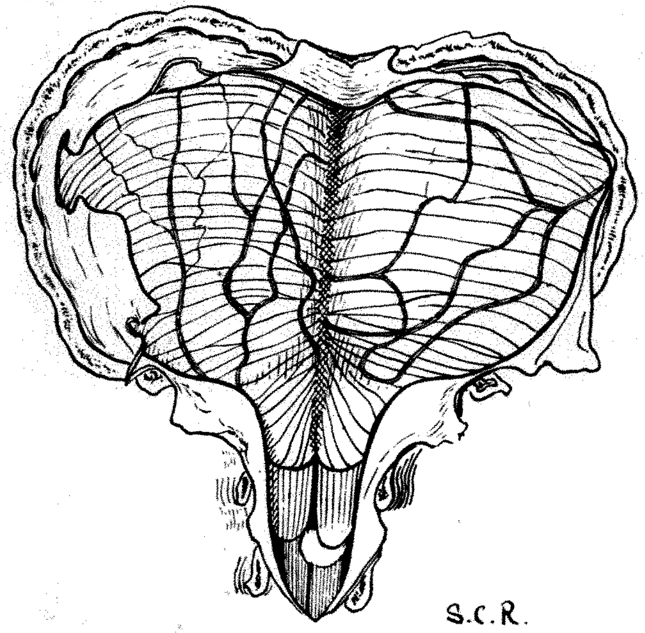

FIG. 4.

Examination.—The patient was thin, mentally alert and co-operative. Weight was 8 st. 7 lb. Apart from bilateral papillœdema of 5 D and slight weakness of the left external rectus muscle the cranial nerves were normal. There was slight tremor in both hands and some uncertainty in carrying out the finger-nose test. The knee-jerks were slightly exaggerated and the right plantar response was extensor. The gait was normal. The blood-pressure was 110 systolic, 75 diastolic. Clinical examination of the chest revealed nothing abnormal, but radiography showed numerous discrete opacities which were regarded as typical of miliary tuberculosis.

The diagnosis of tuberculoma of the cerebellum was made, and a cerebellar decompression advised.

March 7.—Ventriculography showed definite internal hydrocephalus involving the 3rd ventricle. The 4th ventricle was not visible.

Under local anæsthesia the usual cerebellar exposure was made and the arch of the atlas removed. There was gross tension. The dura was opened down to the second cervical vertebra. The cerebellar hemispheres were symmetrical. At this stage the appearance of the structures passing through the foramen magnum suggested a tapering bamboo cane with three short segments each of about 1 cm., the thickest segment being the highest. When the arachnoid was opened the upper segment contained the base of a pressure cone which extended down to just above the level of the atlas. The second segment held the continuation of the pressure cone which was thinner and appeared to be marked off from the proximal part, and the third segment corresponded to a lump on the back of the medulla. The tip of the right tonsil was white and firm though thick, while that on the left side was thinner. The tonsils were freed by the division of the arachnoid round them but because of our experiences with other similar cases we did not separate them to look at the ventricle and we did not inspect the upper spinal nerves. Because of the X-ray appearance of the lungs no exploration was made of the cerebellum itself as we thought there would probably be a tuberculoma. A wide decompression was left.

Fig. 4 is an attempt to represent semi-diagrammatically the appearance of the exposed parts.

The patient's temperature reached 99·8° F. each evening for three days after the operation. She was allowed to get up on the tenth day. That evening her temperature rose to 100, and showed a similar rise each evening for five days, when it became steady. Apart from the temperature she made an excellent recovery and left hospital on March 30.

Subsequent reports indicate that she continues to be free from neurological symptoms. Pulmonary symptoms never developed.

The occurrence of these four cases inside three years suggested that similar cases might have been overlooked. We therefore made a search through the pathological museum and discovered a specimen which had not been recognized five years previously.

Case 5.—Male, aged 15. Vomiting, headache, defective vision. Papillœdema. Cerebellar exploration. Autopsy, deformity of medulla.

C. P. was admitted to the Richmond Hospital, Dublin, on August 16, 1933, on account of headache and defective vision.

For two years before admission the patient had attacks of vomiting every two or three weeks. About one month before, he began to suffer from headaches which started in the frontal region and spread to the left occipital region. The headaches lasted for a few minutes and recurred every two or three days. Vision began to fail about a fortnight before his arrival in hospital.

In hospital severe headache and repeated vomiting occurred nearly every morning.

Examination.—The boy was well-built. There was papillœdema of 5 D in the right eye and 6 D in the left. Visual acuity was $\frac{6}{6}$ in each eye and the visual fields were full. The pupils were equal and active. The left external rectus muscle was weak and there was occasional diplopia. Horizontal nystagmus was present and was more marked on looking to the right.

The rest of the neurological examination was negative.

Radiographic examination of the skull showed convolutional atrophy, slight separation of the sutures and some rarefaction of the dorsum sellæ.

August 24.—Ventriculography: There was a gross hydrocephalus involving the lateral and 3rd ventricles. No air was seen in the 4th ventricle. Operation: Cerebellar exposure. There was no fluid in the cisterna magna. The hemispheres were symmetrical and a small area of the vermis appeared between them. The arch of the atlas was removed. A thick pressure cone reached to a point below this level, the left side of the cone being larger than the right. Rather dense adhesions obscured the tip of the left side of the cone and glued the two sides together. When these adhesions were separated there was a free flow of fluid and all tension disappeared. An incision was made into the vermis but no tumour was seen. The impression was that an adhesive arachnoiditis had blocked the passage of fluid from the 4th ventricle and that the pathway had been cleared. The wound was closed. The patient appeared to make a good recovery from the operation and regained full consciousness. About 10.30 that night he was talking cheerfully to the nurse and asked for a drink. At this time the pulse dropped to 60 and the respirations to 10 but inside half an hour they rose to 90 and 20 respectively. The nurse turned away for about one minute and when she turned back the boy was dead, without warning of any sort.

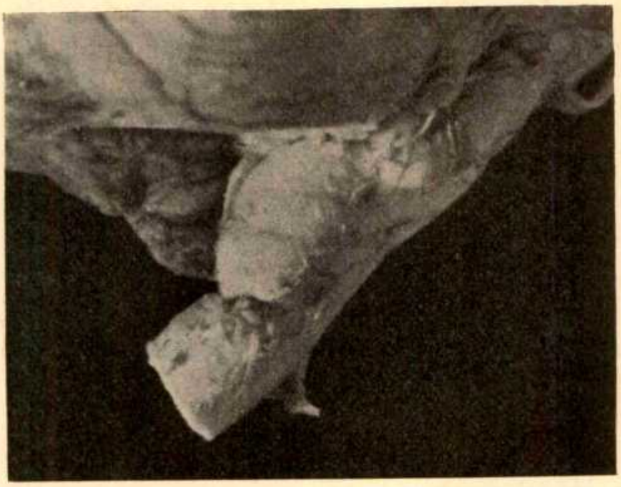

FIG. 5.

Post-mortem examination.—When the pressure cone was elevated the dorsal aspect of the medulla was seen to be heaped up as a lump, and between it and the spinal cord lay a deep groove. There was no corresponding kink on the anterior aspect of the medulla or cord. The medulla seemed to have undergone a certain amount of torsion around its long axis.

The right half of the pressure cone was removed at the level of the foramen magnum. This revealed that the whole closed part of the medulla had lain in the spinal canal (fig. 5).

When the lower part of the cerebellum was dissected off the roof of the 4th ventricle no foramen of Magendie nor foramina of Luschka could be demonstrated. Fig. 6 shows the intact inferior medullary velum from the right side. The 4th ventricle was greatly distended and the aqueduct of Sylvius dilated, as were the 3rd and lateral ventricles. There was no evidence of a tumour anywhere.

Serial sections showed that the lowest part of the 4th ventricle formed a diverticulum overhanging the dorsal aspect of the central canal of the medulla.

The ependyma of the central canal at this level showed proliferation and lower down the canal was completely obliterated by a loose mass of ependymal cells.

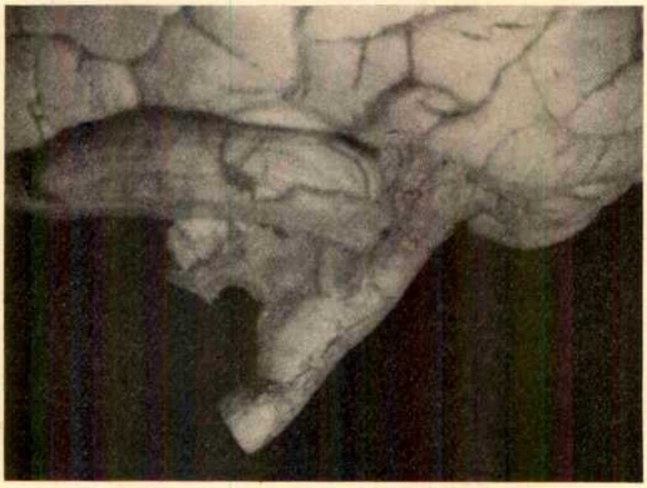

FIG. 6.

ANATOMY.

The anatomical findings in all these cases were very much alike; each had what appeared to be a pressure cone, in each the closed part of the medulla lay in the spinal canal, in each there was a protuberance on the dorsal aspect of the medulla, and in three some obliquity of the upper cervical nerves was noted. All had internal hydrocephalus involving the 4th ventricle. In all cases the protuberance seemed to be chiefly on the right side of the medulla, and in the post-mortem specimens this appeared to be due to the medulla having undergone a slight amount of axial torsion, its lower part being rotated in a clockwise direction. Fig. 7 shows the consequent asymmetry when viewed from in front.

For convenience in description we have used the term "tonsils" to designate the prolapsed cerebellar tissue.

Spina bifida was not demonstrated in any of the cases, but the spine was not X-rayed in cases 1, 2 and 5. In the second case, however, it was examined after death. In Cases 3 and 4 X-ray examination of the spine was negative. Microscopic examination of the medulla (Cases 1, 2 and 5) revealed a certain amount of distortion, as would be expected, but there were no signs of degeneration or demyelinization. In Case 5 proliferation of the ependyma of the central canal of the medulla was present. Cerebellar histology was normal. A search for "torpedo" bodies was carried out by the method recommended by Aring (1938), but none could be found although the axons of the Purkinje cells had apparently been fully stained.

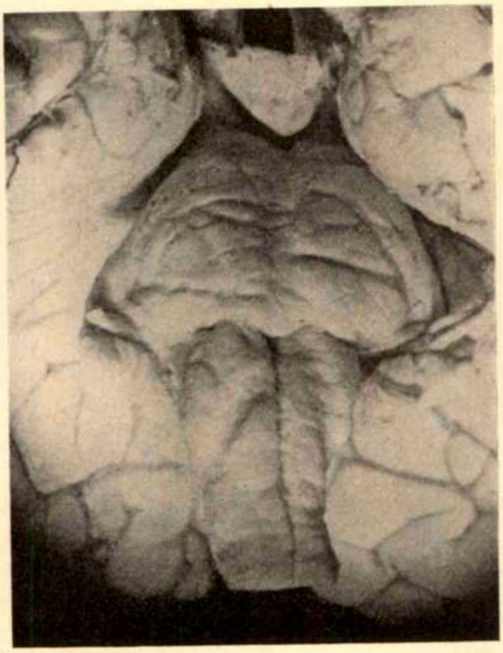

FIG. 7 (*Case* 5).—Anterior view showing the asymmetry and the deep grooves formed by the vertebral arteries.

A clue to the significance of the anatomical findings was furnished by a paper by Russell and Donald (1935). These authors reported ten cases of meningomyelocele associated with a malformation of the hind-brain.

"In this a tongue of variable length, consisting of cerebellar tissue and the greatly elongated medulla oblongata, protrudes downwards into the spinal canal. It overlaps and compresses the upper segments of the cervical cord, distending the dural theca in this neighbourhood and filling the foramen magnum. The cavity of the 4th ventricle extends caudally into this tongue, lying between the cerebellar and medullary components."

"The spinal cord appears abnormally small and the cervical roots always run in a cephalic direction to reach their exits through the dura mater."

"There is a conspicuous hypoplasia of the cerebellum which is usually composed of a small compact mass lacking differentiation into vermis and lateral lobes. The tonsils and flocculi can seldom be identified."

They pointed out that this malformation had been noticed first by Arnold in 1894 and more fully described by Chiari in 1895. Later authors had adopted the name of the Arnold-Chiari malformation.

In one case of meningocele Russell and Donald found that there was caudal displacement of the medulla but that there was no tongue of medullary tissue overlapping the spinal cord as in the fully developed malformation.

We examined six infants with meningomyelocele who had died at or soon after birth. In four of them the fully-fledged Arnold-Chiari malformation was present, but in two the deformity, when exposed as by operation, resembled closely that described in our cases.

The following case came to operation.

Male infant, aged 4 months. Large meningomyelocele. Unsuccessful attempt to close lumbar defect. Cerebellar exposure. Arnold-Chiari malformation. Death.

The infant was healthy and well-nourished. The head was small and the coronal fontanelle just perceptible. There was free movement of both legs. A large meningomyelocele occupied the lumbar region ; it measured about three inches in diameter. The skin over it was tense and purple and there had been some leakage of fluid for two days before admission.

July 1, 1938.—Operation: When the sac was opened the lower part of the spinal cord and the cauda equina were found adherent to its dorsal wall. These structures were dissected free without difficulty and the sac itself was reformed. Fascial flaps were reflected and sutured across the defect and a satisfactory closure of the cutaneous wound was made. By the eighth day enough fluid had escaped beneath the skin to float the wound and it was necessary to aspirate the fluid to prevent undue tension. On the twenty-first day the wound seemed to be perfectly healed and aspiration was stopped, but next day it began to leak. During this time the child had been very well and there had been no sign of raised intracranial pressure.

It was decided to expose the region of the brain-stem in the hope of promoting the return flow of fluid from the spinal subarachnoid space. This was done on July 27 through a longitudinal incision. The foramen magnum was very large and between its dorsal lip and the arch of the atlas there was an interval of about one inch through which the cerebellum protruded. There was no vermis. The arches of the atlas and axis were removed and the opening in the dura continued downwards. Coming from the lower part of the cerebellum was a cone-shaped process of arachnoid which was densely adherent to the prolapsed cerebellar tonsils. These extended downwards to the level of the lamina of the 3rd cervical vertebra. The spinal subarachnoid space was opened at this level and there was a free flow of fluid.

The arachnoid membrane was stripped easily from the lower part of the cerebellar hemispheres, but there was no cisterna magna.

In order to give the cerebellum more room, the back of the foramen magnum was removed for about 1 cm.: this exposed the lateral sinus. The dural incision was extended upwards and to the left. The upper surface of the cerebellum was now exposed and there was a space between it and the tentorium. At this stage there was a sharp hæmorrhage, probably from a cerebellar vein joining the deep aspect of the lateral sinus. This was promptly controlled but it must have been a factor in the child's death soon after the operation.

Post-mortem examination was limited to the region of the operation. The cerebellar tonsils and the medulla at that level were completely surrounded by a deep ring of adherent arachnoid membrane. It was impossible to strip off the arachnoid without tearing the underlying structures. The tonsils in their turn were closely adherent to the back of the medulla except in the middle line where there was a tiny smooth tunnel passing from the 4th ventricle. It seemed as if the tonsils and closed part of the medulla plugged the upper end of the spinal subarachnoid space as the stopper plugs the neck of a bottle. The minute tunnel might be compared to a perforation through the stopper. Simple opening of the dura would have had no effect on the essential lesion.

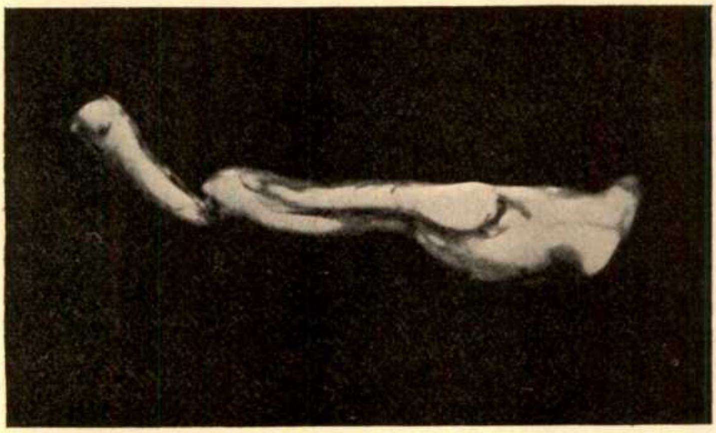

FIG. 8.

These anatomical observations, although unsupported by preoperative tests, tend to confirm the conclusion reached by Russell and Donald that the cerebrospinal fluid can get into the spinal subarachnoid space but cannot get out of it.

The usual protuberance was present on the dorsal aspect of the medulla and there was a corresponding kink on the anterior aspect of the brain stem (fig. 8).

The 4th ventricle was large but not distended, and the aqueduct of Sylvius was small and patent. The upper cervical nerves were oblique.

The operative findings in this undoubted example of the Arnold-Chiari malformation resembled in part those of Case 5. In both the cerebellar cone just covered the closed part of the medulla and concealed the protuberance on the latter; in both the arachnoid membrane was adherent to the cone.

In the true Arnold-Chiari malformation with spina bifida there are many degrees and the lesser degrees recall the conditions found in our five cases. In these cases, however, the unstrippable adhesions, which were constant in the infants, were never found. Until the whole spinal canal can be opened up and the spinal cord examined in some similar case it is impossible to express an opinion on the real relationship of these cases to those of the Arnold-Chiari malformation.

Clinical Features.

The chief symptoms and signs of our cases are presented in the following table:—

Case	1	2	3	4	5
Age...	18	10	32	26	15
Headache	+	+	+	+	+
Vomiting	+	—	+	—	+
Papillœdema	+	—	—	+	+
Ataxia	left side	++	++	arms	—
Exaggerated reflexes ...	+	+	—	+	—
Babinski	—	+	—	R.	—
Nystagmus	—	++	—	—	+
Cranial nerve weakness	R. 9 and 12 L. 11	L. 6	—	L. 6	L. 6

There was no uniform symptomatology in these cases, and nothing that would suggest the presence of this condition in a new case. On one occasion we made a tentative preoperative diagnosis, but syringobulbia was demonstrated later.

In general, except in Case 1, the clinical aspect of these cases was that of obstructive internal hydrocephalus without localizing signs.

Ventriculography was disappointing: although the 4th ventricle was grossly dilated in all the cases, it was visible in two only.

Surgical Considerations.

Recognition.—It may not be easy to recognize this condition at operation if the cerebellar tonsils are thick and completely cover the medulla, as in Case 5. Suspicion should be aroused if the arachnoid is adherent to the tonsils or if the tonsils themselves appear flatter than they usually are in a pressure cone, or if they are feathery or white.

If the protuberance on the dorsal surface of the medulla is seen, the suspicion is confirmed, but if it is not, obliquity of the upper cervical nerves should be looked for. Of course the presence or history of spina bifida would be significant.

Problem of treatment.—In the first two cases the arachnoid membrane was widely opened from the cisterna magna to the spinal subarachnoid space. It was not adherent to the tonsils. The latter were separated from each other and lifted from the medulla in order to open up the 4th ventricle. This manipulation was easy, and the separation bloodless, and at the end of the operation the tonsils lay loosely where they had lain at the beginning. Both patients died: one in forty-eight hours, the other in eight. Microscopic examination did not reveal any cause for the fatalities.

In the next two cases, when the arachnoid was widely opened as before and the condition recognized, nothing more was done. Both patients survive and are well.

Case 5 differed from the others in two respects. First, the arachnoid was adherent to the tonsils ; and second, the 4th ventricle was closed. The arachnoid was dissected off the tonsils and the latter were mobilized. Neglect to open the 4th ventricle was a serious error. The patient died in ten hours. In the infant with the meningomyelocele the spinal cord was freed from its attachment to the sac at the first operation and later the subarachnoid space was opened widely above and below the band of adherent arachnoid which encircled the cerebellar cone and the medulla. The cone was not touched. We think that this infant died because of hæmorrhage during the operation.

In the light of these results, it would seem that the safest thing to do is to open the arachnoid widely from the region of the cisterna magna to the spinal subarachnoid space and to do nothing more. If the arachnoid is adherent to the tonsils, it should be left adherent, and the subarachnoid space opened above and below. The tonsils should not be mobilized.

If there is no outlet from the 4th ventricle as in Case 5, and if mobilization of the cerebellar tonsils is as dangerous as we think it is, it would seem necessary to split the vermis, or to short circuit the cerebrospinal fluid by opening the 3rd ventricle.

These therapeutic speculations apply only to the degrees of the malformation that we have described, for there are probably many other degrees which we have not met with and which may present different surgical problems.

SUMMARY.

A deformity of the brain stem and cerebellum in children and adults is described. It is suggested that this deformity is a minor degree of the Arnold-Chiari malformation found in association with meningomyelocele.

Tentative suggestions for treatment are advanced.

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FAMILIAL NEUROMYELITIS OPTICA: ITS OCCURRENCE IN IDENTICAL TWINS.

BY DOUGLAS McALPINE.

(From the Department of Nervous Diseases, Middlesex Hospital.)

The condition known as neuromyelitis optica is still of sufficient rarity to merit attention, not only on clinical and pathological grounds, but also because its relationship to other members of the demyelinating group of diseases remains uncertain. No example of familial neuromyelitis optica has been reported in the literature. This paper contains an account of this disease, as it occurred in identical twins.

Alice K. and Dorothy K. were born on September 8th, 1909; there was one placenta. When four months old they both suffered from bronchitis, at six years from measles, and at eighteen years from chickenpox. The onset of menstruation occurred at the same time in both. In their facial appearance, colouring, body configuration, temperament, scholastic and games ability they were alike.

The following is an account of the illness which proved fatal to them both.

Case 1.—Female, aged 24. Following "influenza" developed an acute dorsal myelitis; subsequent improvement. Five months after onset blindness and recurrence of dorsal myelitis with spread to cervical cord. No return of vision. Bed sores and a bladder infection led to death eighteen months after onset.

Alice K., aged 24, on January 16, 1933, developed a cough without sore throat which was thought to be "influenza". On January 20 she experienced severe pain across the shoulders which persisted for several days. On January 26 she noticed tingling in the left thigh followed by numbness which spread upwards to the abdomen and then affected the right leg in the course of three days. On January 27 the legs became weak and she had retention of urine which lasted for two days. On January 30 she was admitted to the Neurological Ward of the Middlesex Hospital. The temperature was normal. She was an intelligent patient. The cranial nerves and upper limbs were normal. There was paresis of the lower intercostal and abdominal muscles and of the lower limbs, the right leg being more affected than the left. The abdominal reflexes were absent; the left knee-jerk was slightly increased, whilst the right was diminished. Both ankle-jerks were brisk. The plantar responses were extensor;

a flexion withdrawal reflex could easily be elicited. All forms of sensation were diminished on the trunk below the 4th dorsal segment. Tactile sensation was unimpaired on both legs ; thermal and pin-prick sensation were retained below the 3rd lumbar segment on the right side, but were absent on the left leg. Vibration sense was absent, but postural sense was normal. There was retention of urine and incontinence of fæces. A lumbar puncture showed a clear fluid ; the Wassermann reaction was negative, 4 lymphocytes per c.mm., protein 0·03 per cent., Lange colloidal gold curve 1111222100.* On February 3 the paraplegia was more marked. Both knee-jerks were now absent, whilst the ankle-jerks remained brisk. Thermal and pin-prick sensation were now lost in the right leg, but postural sense remained unaffected. During the course of the next three days the paralysis in the lower limbs became almost complete. However, by the end of February, power had improved in the left leg, and the knee-jerks were feebly present. Thermal and pin-prick sensation returned in the right leg and later in the left leg. Vibration sense remained impaired up to the beginning of April, whilst postural sense was retained, except on two consecutive days. Sphincter control returned, and the patient was discharged on May 4 with a moderately severe spastic paraplegia which, however, did not prevent her from walking with the aid of sticks.

Improvement continued for one month. On June 20 she noticed blurring of vision in the right eye and, within two days, the vision in both eyes had rapidly failed. On June 27 she experienced severe pain in the abdomen with recurrent vomiting. On June 29 the legs became weaker, and on June 30 there was loss of sphincter control. On July 3 she was readmitted to hospital. In addition to the above symptoms she now complained of tingling in the arms. The temperature was 101° F. Both pupils were dilated and responded slowly and incompletely to light. Vision in both eyes was reduced to perception of light. The fundi appeared normal, apart from fullness of the veins. The remaining cranial nerves were normal. There was no loss of power in the upper limbs, or alteration in the reflexes, but thermal and pain sensibility was lost between segments cervical 6 and dorsal 1 on both sides, other forms of sensation being normal. There was complete paraplegia in extension with a well-marked flexion withdrawal reflex. All forms of sensation were lost below the 3rd dorsal segment. On July 5 the loss of thermal and pain sensation extended up to the 4th cervical segment on both sides and both hand-grips became weak. On July 8 the arm reflexes were absent, and there was marked weakness of both hands and wrists. On July 7 the dissociated sensory loss was found up to the 3rd cervical on the left side, and power was now diminished at both elbows, and slightly at the shoulders. There was, for the first time, slight postural loss in both hands with diminution of vibration sense, and this loss became complete in the course of the next twenty-four hours. No definite weakness of the diaphragm was apparent. On July 8 she could count fingers with the right eye, but had only perception of light with the left eye. Subsequently complete blindness developed with double optic atrophy. Power partially returned in both arms, but to an insignificant extent in the lower limbs, which passed into paraplegia in flexion. Subsequently there was some return of sensation in the upper limbs, but anæsthesia remained complete on the trunk and lower limbs. Despite an in-dwelling catheter and frequent bladder wash-outs, the urine became heavily infected and she developed bed sores. A lumbar puncture on January 3, 1934, showed 5 cells per c.mm., protein 0·03 per cent., Lange curve normal. She remained totally blind and in a chronic state of paraplegia inflexion. The bed sores extended and she died on August 10, eighteen months after the onset of her illness.

Case 2.—Female, aged 26, following a cold rapid onset of dorsal myelitis with spread to cervical cord; slow improvement from severe quadriplegia. Nine months after onset bilateral blindness, permanent in right eye. One year later fresh attack of myelitis, rapidly fatal. Duration of illness twenty-six months.

Dorothy K. On February 29, 1935, when aged 25, she had a tooth extracted under gas and felt indisposed for a few days. On March 9 she developed a cold but no sore throat. During the night of March 13 she began to suffer from a very acute pain in the region of the shoulder blades, and on the morning of March 14 she felt that she had been beaten with sticks across the back. On the morning of March 16, on getting out of bed, she noticed that she could not feel the cold of the linoleum with the left foot. This was succeeded by a dead and heavy feeling which spread up the left leg, and by the following day it had reached the abdomen. On March 18 the right leg felt numb, but she was still able to walk quite well. She noticed slight hesitancy in micturition on this date. On March 20 her legs were weaker and she had retention of urine. The pain had been severe enough to keep her awake at nights, and on the day of admission she had felt an aching pain across the back of the neck. On March 21 she was admitted to the Neurological Ward of the Middlesex Hospital. A striking similarity in facial appearance and colouring between this patient and her sister was noticed. She was equally intelligent, and since she had visited her sister many times in hospital, she was familiar with the symptoms and course of her disease. Yet throughout her own long and distressing illness she displayed the greatest fortitude. Her temperature was normal. The throat was markedly congested. The pupils and fundi were normal. There was no nystagmus and vision was full. The remaining cranial nerves were normal. Power, reflexes and sensation were normal in the upper limbs. The abdominal reflexes were absent. There was a moderate paresis of both lower limbs, more especially of the right one. The deep reflexes were depressed. The right plantar response was extensor, the left equivocal. There was complete loss to pain and thermal sensation on the abdomen below the level of D.6, and on the lower limbs. Tactile and vibration sense in the lower limbs and postural sense in the toes were normal. There was retention of urine. The cerebrospinal fluid was clear. The pressure was 130 mm. of water. Cells 2 per c.mm. Total protein 0·025 per cent. Colloidal gold curve negative. On March 24 the patient appeared drowsy. The temperature was 101·2° F. She complained of pain in both arms and around the neck. There was paresis of both arms, more especially the left. The arm reflexes were increased. There was diminution of pain and thermal sensation in the right arm, and hyperæsthesia in the distribution of the 3rd and 4th cervical segments. On March 27 the pains around the neck were more marked and signs of a paresis of the left cervical sympathetic were noted. No movements of the fingers of the left hand were possible, and those at the elbow joint were weaker, while there was now definite weakness of abduction at the shoulder joint. The same distribution of paresis was present in the right arm, but to a lesser degree. The reflexes in the left arm were diminished. There was a complete flaccid paraplegia of the lower limbs with absent deep reflexes. A definite band of hyperæsthesia was present at the level of C.3. Pain and thermal sensibility were lost below C.3 on both sides, whilst postural and vibration senses were lost on the left hand, but were normal on the right side. All forms of sensation were now lost below D.2.

On April 2 the left arm was completely paralysed, and also the right arm, apart from a feeble movement of abduction at the shoulder. Breathing was mainly carried out by the extraordinary muscles of respiration, although at no time had the diaphragm become completely functionless. Postural loss became complete in the joints of both upper limbs. About a fortnight later power began to return in the arms and proceeded slowly. Pain and thermal sensibility returned rapidly but postural loss and tactile sensation remained impaired in the hands, and did not return until July, 1935. There was no return of power in the lower limbs, and a condition of paraplegia in flexion developed, which was overcome, to a certain extent, by the use of splints. An in-dwelling catheter was used from the beginning and an automatic method of draining the bladder was employed ; the urine, however, became heavily infected. Pain and thermal sensibility returned on the trunk and thighs, but remained impaired below the knees. Postural and vibration senses remained lost in the lower limbs. She was discharged to another hospital on September 29, 1935. She was then able to use her hands quite well, but remained completely paraplegic, with no control over her bladder. About December 7 she noticed a large spot in front of the left eye. The vision further deteriorated during the next two weeks. On December 25 she noticed failure of vision in the right eye, which progressed rapidly until she became blind in both eyes. She had experienced no pain in the eyes, or headache.

On January 10, 1936, the patient was readmitted to the Middlesex Hospital. Both pupils were dilated and reacted poorly to light, especially the right. She was able to count fingers with the left eye, whilst with the right eye there was only perception of light. The temporal half of the left disc was pale. The margins of the right disc were fluffy and the veins were engorged. There was a large central scotoma in the left eye. Further improvement in the power of the arms, with slight return of power in the lower limbs, had occurred since her discharge from hospital in October, 1935. There was a marked degree of adductor spasm and a tendency to a paraplegia in flexion. Postural loss was still marked in the distal joints of both feet. There was incontinence of urine with a heavy bacilluria. An indwelling catheter with an automatic washout was again instituted, and mandelic acid given by the mouth. The vision slowly improved in the left eye, so that by the time she was discharged in May, 1936, she could read small print with this eye, but could only count fingers with the right. Both discs were now atrophic. Power had returned sufficiently to the lower limbs to permit of her standing and taking a few steps with support. The bacilluria disappeared, and useful control of the bladder returned, so that she was rarely incontinent. When seen again in September, 1936, she was able to walk alone with the support of two sticks. No further improvement in vision had occurred. She remained in this condition until the beginning of May, 1937, when she complained of pain and numbness around the neck, and she again became incontinent. She was readmitted to the Middlesex Hospital on May 5. She was still able to read small print with the left eye, and count fingers with the right. Both discs were atrophic. There was marked paresis of the left arm and renewed weakness of the lower limbs, left more than right. There was loss of pain and thermal sensibility, and slight impairment of cotton-wool sensation in the distribution of C.3 to 7 on the left side, and on the right arm below C.4. Postural sense in the fingers was intact, and vibration sense was normal. On the trunk there was diminution to all forms of sensation below D.2 on the right side, and D.4 on the left side. She vomited frequently and became drowsy. The pain around the neck continued. The right arm became paralysed. Postural loss became complete in both arms and pain and thermal loss extended up to C.2. The diaphragm became paresed, and she died of respiratory failure on May 20, twenty-six months after the onset of the disease.

PATHOLOGICAL FINDINGS.

The usual methods of staining were used in both cases. Sections from various parts of the hemispheres, basal ganglia, brain stem and cord were examined. Unfortunately, the optic chiasma from Case 1 was not available for study.

Case 1.—On naked eye inspection of the meninges of the brain and spinal cord, nothing abnormal was noted. However, when the cord was sectioned it was obvious that there was a diffuse pathological process in the mid-dorsal region; there was no differentiation between the white and grey matter, and the cut surface appeared dark brown in colour. Microscopic examination of the cortex, sub-cortical white matter and the basal ganglia, showed no evidence of demyelination or of round-celled infiltration. The mid-brain, pons and medulla were similarly normal. A portion of one optic nerve was available. It showed well marked demyelination in its centre (fig. 1). There was no perivascular or meningeal infiltration. Spinal cord: There was a diffuse demyelination extending from the mid-cervical region to the lower part of the dorsal cord. It was most intense in the cervical enlargement and mid-dorsal region. In the mid-cervical region there was well-marked demyelination of the posterior part of the cord, extending anteriorly to involve both the direct pyramidal tracts, and on one side the antero-lateral part of the cord

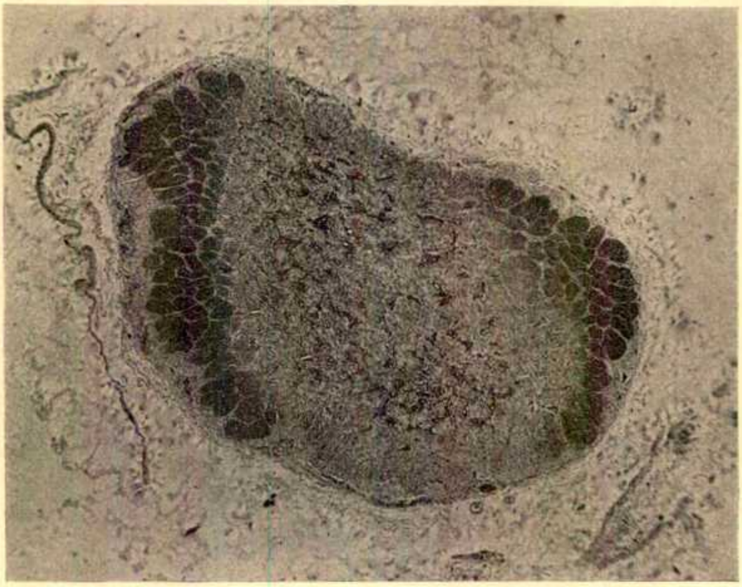
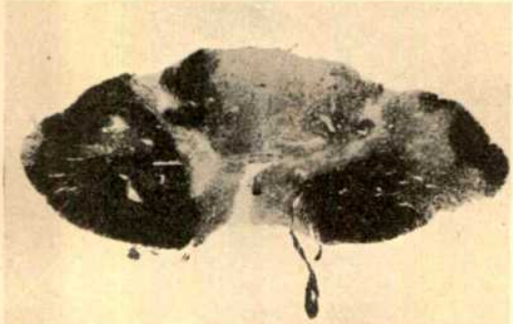


FIG. 1 (*Case 1*).—Diffuse demyelination in centre of optic nerve. Scharlach R. and Hæmatoxylin.

(fig. 2). In the upper dorsal cord demyelination extended outwards from the centre of the cord, mainly in an anterior and lateral direction (fig. 3). From the 5th to the 8th dorsal segments there was almost complete demyelination of the whole cord. Normally staining fibres occurred in a few isolated bundles, but the remainder had disappeared. In the lower dorsal and lumbar cord the myelin sheaths showed no appreciable changes, except in the pyramidal tracts, due to a Wallerian degeneration. The axis cylinders showed changes varying from degeneration to destruction in the affected parts of the cord. Perivascular infiltration was conspicuous by its absence throughout the cord and meninges. Microglial reaction was marked in the affected portions of the cord in the form of fat-laden corpuscles and cells with rod-shaped nuclei. Macroglial reaction was moderate considering the age of the lesions. It was slight in the cervical, but somewhat more marked in the mid-dorsal region, more especially towards the periphery of the cord. The blood-vessels showed no evidence of arteritis. There was a slight increase in the number of capillaries in the mid-dorsal region.



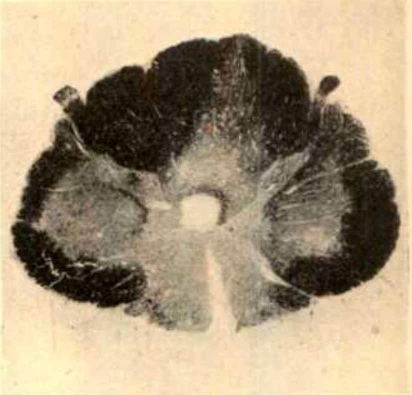


FIG. 2 (*Case 1*).—Mid-cervical region (see text). Weigert-Pal.
FIG. 3 (*Case 1*).—1st dorsal segment (see text). Weigert-Pal.

Case 2.—The cut surfaces of the cord showed a greyish softening from the cervical region to the middle of the dorsal cord, similar to that observed in Case 1, but more marked in degree. The histological changes were confined to the optic chiasma, optic tracts, optic nerves and to the spinal cord. No demyelination or perivascular infiltration was observed in sections from various parts of the cortex, basal ganglia, ventricular walls and brain stem, with the exception of the lower medulla, where two small recent areas of demyelination with round-celled infiltration were found in its dorsal part. The optic chiasma was cut in serial sections. A diffuse demyelination was present extending into both optic nerves and the left optic tract. The demyelination at certain levels was not complete and bundles of normally staining fibres were present (fig. 4). The majority, however, showed changes varying from complete disappearance to fragmentation and ballooning. In the centre of the chiasma, in the more caudal sections, the process had advanced to necrosis. With the exception of a small, rather sharply delimited, area in the right optic tract, the demyelinating process was a diffuse one. Perivascular infiltration on the whole was slight; when present, the cells were mainly fat granule corpuscles, with a few lymphocytes. Sections of the optic nerves showed a diffuse demyelination at the centre of each nerve. Spinal cord: There was a diffuse demyelination extending from approximately the 2nd cervical segment to the 10th dorsal segment. The process was most intense in the cervical enlargement, and the mid-dorsal region. In the cervical region demyelination diffusely affected the cord, sparing only the anterolateral tracts on one side. From segments C.5 to 8 there was necrosis and cavitation in the centre of the cord. In the 1st and 2nd dorsal segments the process was more widespread than in the cervical cord, being especially intense in the centre of the cord, where it extended outwards, only sparing parts of the anterolateral tracts (fig. 5). From the 4th to the 6th dorsal segments the lesion was at its maximum; demyelination was complete, except for a few scattered bundles of fibres. The centre of the cord was necrotic (fig. 6). At the level of the 8th dorsal segment demyelination was less complete, being more marked in the posterior than in the anterior half of the cord. Degeneration of the pyramidal tracts was symmetrical. In the lower dorsal and lumbar cord there was a descending degeneration of the pyramidal tracts. The axis cylinders were considerably affected, especially in the cervical and mid-dorsal regions. Many of the fibres seemed to have been destroyed, whilst others showed gross changes including fragmentation, swelling and end bulb formation. In the less affected areas many of the axis cylinders were normal. Microglial reaction was marked; fat granule corpuscles were abundantly present in the affected portions of the cord. Cells with rod-shaped nuclei were more frequent at levels where the lesion was moderate or slight in degree. Macroglial reaction was poor; gliosis on the whole was conspicuous by its absence. In the mid-dorsal region, where the necrotic process was most marked, a few astrocytes were seen situated at the periphery of the cord; the majority shewed degenerative changes such as swelling of the cell body. Perivascular infiltration was marked in the cervical cord, more especially around the branches of the anterior spinal artery. The cells were mainly lymphocytes. There

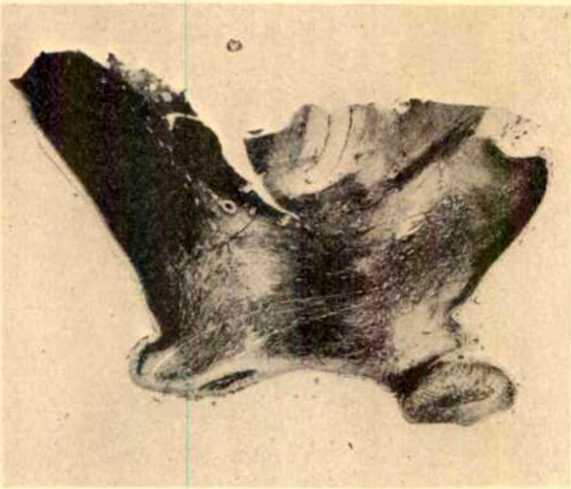


FIG. 4 (*Case 2*).—Optic chiasma (see text). Weigert-Pal.

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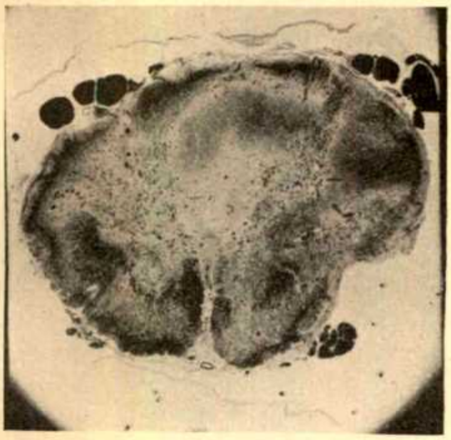

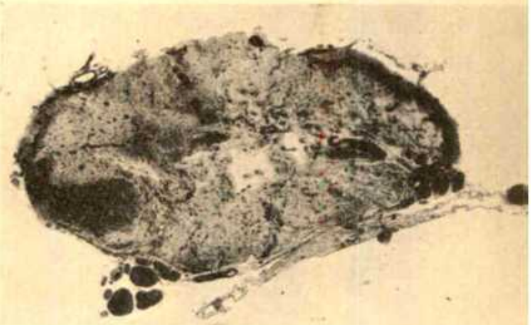

FIG. 5 (*Case* 2).—2nd dorsal segment. Diffuse demyelination. Weigert-Pal.

FIG. 6 (*Case* 2).—6th dorsal segment. Diffuse demyelination with necrosis and cavitation in the centre of the cord. Weigert-Pal.

A COMPARISON OF THE TWO CASES.

The clinical picture on the whole was strikingly similar in these twins. In each a " cold " preceded the first symptom of myelitis. Severe pain across the upper back, tingling and numbness in the left leg ascending to the abdomen and then affecting the right leg, was the sequence of the sensory disturbance in both cases. Each patient was admitted on the tenth day of her illness and each showed signs of a severe mid-dorsal myelitis. In both cases the right leg was weaker than the left. In Case 1 thermal and pinprick sensation were at first only lost on the left leg, whilst in Case 2 the initial sensory loss on both lower limbs was confined to these forms of sensation. The rest of the examination of the nervous system, including vision, was negative in both cases at this stage. The cerebrospinal fluid was normal throughout the illness in both cases, except that on the first occasion Case 1 showed a mild Lange colloidal gold curve. The course of the disease was now different. In Case 1 the myelitic process, although becoming more severe, remained localised to the dorsal cord. Slow improvement occurred and four months later she was discharged from hospital able to walk a little and having regained to a large extent control of her bladder. In Case 2, within three days of admission the cervical cord became affected. It is interesting to note that thermal and pin-prick sensation were affected in the right arm, whilst other forms of sensation remained normal for a few days. This patient passed through a stage of quadriplegia, but subsequently power began to return in the upper limbs, but scarcely at all in the lower limbs, even after six months in hospital. Blindness marks the next phase of the disease in both cases. In Case 1, one month after her discharge from hospital and five months after the onset of the illness, loss of vision was noticed, first in the left eye ; within one week she was blind in both eyes except for the perception of light. In Case 2, ten weeks after leaving hospital and nine months from the onset, vision failed in the left eye, and eighteen days later in the right eye. The third phase in each case was a fresh myelitis. In Case 1 this accompanied the onset of blindness, a fresh dorsal myelitis occurring which spread to the cervical cord, resulting in a quadriplegia which became chronic, the patient finally dying of bed sores and a severe bladder infection. In Case 2 the second attack of myelitis did not occur until a year later ; it affected the cervical cord and rapidly proved fatal. If these events are summarized in the two cases, it will be seen that in Case 1 the duration of the illness was eighteen months, and in Case 2 twenty-six months. In both cases there were two distinct attacks of myelitis. In both cases the ocular symptoms and signs were very similar, failure of vision beginning in the left eye, and later going on to blindness. In Case 1 there was no appreciable return of vision, whilst in Case 2 vision in the left eye returned sufficiently to enable the patient to read. Both cases shewed a central scotoma initially. In Case 2 there was an unilateral papillitis. The final picture in both cases was one of optic atrophy.

The pathological process in both cases was limited to the cord, optic chiasma, optic tracts and optic nerves. No change of importance was found in the cerebral hemispheres, in the walls of the lateral ventricles or in the brain stem, with the exception of two recent areas of demyelination in the dorsal part of the medulla in the second case. The optic nerve in Case 1 shewed well-marked demyelination. In Case 2 there was a diffuse demyelination of the optic chiasma, optic nerves and the initial portion of one optic tract. In both cases there was a diffuse myelitis extending from the cervical region through approximately two-thirds of the dorsal cord. In both cases the macroscopic appearance of the cord was striking. In the mid-dorsal region, over several segments, the cut surface of the cord appeared dark brown in colour. The substance of the cord was soft and diffluent, and there was no distinction between the white and grey matter. In the cervical cord demyelination in both cases affected particularly the dorsal half of the cord, the process spreading outwards from the region of the central canal. In the mid-dorsal region demyelination was nearly complete in both cases. In the cervical enlargement in Case 2 and in the dorsal cord in both cases, the process had advanced to necrosis. In Case 2 atrocytes were scarce, except at the periphery of the cord, and gliosis was absent or slight. In Case 1 the macroglial response was more definite, especially in the less affected portions of the cord. In both cases there was a brisk microglial response in the form of fat-laden corpuscles and cells with rod-shaped nuclei. Perivascular and meningeal infiltration with lymphocytes was evident at most levels of the cord in Case 2, but was absent in Case 1. The anterior horn cells in the cervical and dorsal cord shewed changes ranging from complete destruction to varying degrees of chromatolysis. Capillary overgrowth was a feature of Case 2, but was slight in Case 1.

DISCUSSION.

Clinical diagnosis.—Neuromyelitis optica, though somewhat variable in its effects on the nervous system, shows certain distinctive features. The age incidence varies from five to over sixty years ; the disease is, however, commoner in the early decades of life. Constitutional symptoms are not uncommon at the onset, especially headache, sore throat and a raised temperature. After an interval of a few days, or, more rarely, several weeks, the first symptoms of invasion of the central nervous system shew themselves. According to Beck (1927) 75 per cent. of cases shew failing vision as the first sign of the disease, and subsequent writers agree that this is the usual mode of onset. In the remaining cases, symptoms of a myelitis are the first to declare themselves. Where blindness first appears, signs of a myelitis may follow at an interval of some hours, weeks, or rarely, months. The same intervals may occur between the myelitis and the first signs of failing vision. Blindness may be first noticed in both eyes, or affect each eye at an interval of a few days, or rarely, two or three weeks. As a rule the failure of vision is extremely rapid, so that in a few days there may remain only perception of light. In such cases the pupils are usually dilated and react sluggishly to light. The discs may be normal, or there may be a papillitis, unilateral or bilateral. Vision may be so reduced that charting of the visual fields is impossible. Where the loss of vision is less sudden or less complete it is usually possible to establish the presence of a large central scotoma. Homonymous defects may co-exist, or at first constitute the only perimetric change. Partial recovery of vision may occur, especially in those cases that survive some weeks or longer. This recovery may be unilateral or bilateral. In other cases varying degrees of blindness remain. The discs in the later stages are atrophic. Diplopia and nystagmus are conspicuous by their absence. It is true that in isolated cases these signs have been observed, but their continued presence should throw doubt upon the diagnosis of neuromyelitis optica. In the majority of cases the dorsal portion of the cord is first attacked. Pain is commonly the earliest symptom, being referred to the back, between the shoulders, in a girdle distribution, or in the legs. It is frequently described as sharp or shooting and may be severe. Numbness and tingling are the usual forms of paræsthesiæ which follow in either one or both lower limbs, spreading upwards to the abdomen. Within a few hours or days weakness of the lower limbs is noted, and retention of urine follows. In the acute cases the deep reflexes are depressed or absent, whilst in those cases in which the onset is more insidious they are exaggerated from the commencement. Muscular wasting has been reported, usually in the upper limbs, in a few of the more chronic cases. Sensory loss as a rule does not differ from that found in other forms of acute myelitis. In the initial stages the upper level of sensory loss usually lies between the upper and mid-dorsal regions. There may be a zone of hyperæsthesia. In both the cases reported in this paper there was an initial stage in which pain and thermal sensibility were alone affected for a few days. A similar dissociated loss has been observed in other cases. [Balser (1936), Milian, Lhermitte, Schaeffer and Horowitz (1931), Dollfuss (1928).] This stage is only a temporary one and is followed by loss of tactile and deep sensation. With rare exceptions the disease spreads to the cervical cord. In the rapidly progressive cases this extension occurs at a short interval after the first sign of the dorsal myelitis. Death usually takes place as a result of respiratory failure, more frequently from paresis of the phrenic nerve than from extension of the process to the medulla. Temporary recovery is possible even after involvement of the cervical cord, as evidenced by Case 1. In the more chronic type of case, with remissions, an interval of weeks or months may elapse before the cervical cord is affected. Emphasis has already been laid on the rarity of nystagmus and diplopia in this disease. In addition to these, euphoria, paresis of cranial nerves (with the occasional exception of the 10th), tremor or ataxia, do not occur, even in the more chronic cases.

Cerebrospinal fluid.—Certain characteristic findings occur. In over 50 per cent. of cases, and in a higher percentage in the rapidly progressive type, there is an increase in cells, mainly polymorphonuclear in type. The protein is moderately raised. The Lange and benzoin curves are almost constantly negative in all stages of the disease. This association of a cell increase and a negative colloidal curve would appear to be characteristic of neuromyelitis optica.

Of the cases occurring since the publication of Beck's (1927) paper twenty-two cases, including the two described in this paper, have been analysed as to their course; they would appear to fall into three groups. (1) Those cases which follow a progressive course, death occurring in from five days to several weeks. Ten of the cases came into this group. (2) Cases which shew one or more remissions, but finally die after some months up to two or three years. There were seven cases that followed this course. (3) Cases which recover completely or partially, of which there were five examples. It is doubtful whether these cases have been followed sufficiently long to justify a diagnosis of neuromyelitis optica; some of them may eventually prove to be suffering from disseminated sclerosis.

Pathological diagnosis.—Neuromyelitis optica is characterized by a severe demyelinating process which affects the optic chiasma, optic nerves, optic tracts, and the spinal cord. There is a relative escape of the brain and brain stem. Beck, in 1927, collected twenty-five cases in which pathological examinations had been performed. Nine of these showed disseminated foci, whilst in sixteen there was evidence of a diffuse myelitis. The present writer has collected a further twelve pathological reports since the publication of Beck's paper, including the two cases which are the subject of the present paper. In nine of these the myelitis was diffuse, whilst in the remaining three there were disseminated foci. A diffuse demyelination would therefore appear to be the characteristic lesion in neuromyelitis optica. A further hallmark of the disease is necrosis, sometimes accompanied by cavitation; this occurs almost constantly when the myelitis is diffuse. On the other hand, those cases in which there are disseminated foci seldom show this change. There is considerable variation in the histological details in this disease. This is understandable when such factors as the varying duration of the illness, and, in the chronic cases, the absence or presence of an exacerbation of the disease shortly before death, are considered. The following summary is based upon twelve recently published cases. In the areas most affected, more especially in those that are necrotic, destruction of axis cylinders is usual. Of those that survive, the majority shew degenerative changes, whilst a few remain unaltered. When the myelitis is less intense the axis cylinders are less altered, and some may be normal. As might be expected from the variation in the intensity and duration of the morbid process, the response of the neuroglia is inconsistent. Of three cases reported by Balser, in only one of them was the glial proliferation more than slight. In a case reported by Hassin (1937), astrocytes were comparatively scarce, chiefly occurring at the edge of the affected areas. The fibrous astrocytes were especially rare and often shewed a breaking up of their processes. Marchiewicz and Peters (1936) and Gozzano (1937) comment on the relative absence of gliosis. On the other hand, Milian and his collaborators (1931) report a case in a male aged 37 in whom death occurred at the end of five weeks. Disseminated foci were found in the cord and chiasma. None of the lesions were necrotic. There was a definite increase of macroglial elements. These authors believe that in this case there was a double process, destructive and reactional, resulting in a hyperplasia of the macro- and micro-glial elements. Cestan, Riser and Planques (1934) have reported a case in a male aged 50 who suffered from hypertension. He developed an aphasia and later a quadriplegia which improved. This was followed by failure of vision with papillitis. Again there was improvement. The patient died finally from uræmia eleven months after the onset. Several thrombotic softenings were found in the brain, and in addition disseminated foci, greyish in colour, which the authors consider to be precisely the same as those found in disseminated sclerosis; none of these shewed necrosis. There was a marked increase in the number of astrocytes. This case is atypical, not only because of the co-existence of cerebral vascular disease, but also by the occurrence of foci of demyelination in the brain stem and hemispheres. In both these cases there were disseminated foci and necrosis had not occurred. It would seem to the writer that the variations in the response of the macroglia in this disease to a large extent depend upon the intensity of the lesion. When necrosis occurs the astrocytes are not even spared, and therefore a subsequent gliosis is not possible, except at the margins of the affected areas. On the other hand, the microglia uniformly show a marked reaction, more especially in the form of fat-granule corpuscles; their other derivative, namely, cells with rod-shaped nuclei, are scarce in the necrotic areas, but are plentiful where the process is less acute. With regard to evidence of an inflammatory reaction, here again the findings vary considerably. In Balser's first case, perivascular infiltration with lymphocytes and plasma cells was found, especially in the chiasma. The duration of the illness was nine weeks. In his second case, which lived for five months after the onset, a similar degree of inflammatory reaction was found. In the case reported by Uréchia and Veluda (1934) in which death occurred in the short time of five days after the appearance of the first symptom, a diffuse inflammatory lesion, especially in the neighbourhood of blood vessels, was present throughout the cord, chiasma, and optic nerves. The meningeal vessels were infiltrated with polymorphonuclears, lymphocytes, and plasma cells. In the chronic relapsing type of case evidence of any inflammatory change may be slight or absent, as in a case reported by Hassin, and in the two cases described in the present paper, in the second of which mild inflammatory changes could be explained by a recent exacerbation shortly before death. It would appear that a true inflammatory reaction usually occurs in the acute phases of the disease, but is slight or absent in the more chronic cases. The grey matter may be affected as much as the white matter, and several of the reported cases have shewn destruction of anterior horn cells when the lesion has been severe. There seems a predilection for the central grey matter to be particularly affected, and it is in the region of the central canal that cavitation may occur. A considerable increase in the number of capillaries has been noted by Balser in two of his three cases, and by Hassin and Beck. It was a feature of Case 2 in this paper. Such changes, however, seem to be relatively uncommon. Two conditions seem necessary for this change. Firstly, a duration of the illness for some months; for example, in Hassin's case, which lived for fifteen months, the capillary overgrowth, judging from the illustration in his paper, was as well-marked as in the present Case 2, who lived for twenty-six months. Secondly, in all the cases in which this feature has been present, necrosis of the cord has occurred. It would seem logical to assume that the destruction of astrocytes, which results from the necrosis, and the consequent poor glial reaction, leaves only one tissue in a position to effect repair, namely the blood vessels. At the same time, one would have also expected a marked fibroblastic reaction. This, however, occurs less frequently than the capillary overgrowth, although in a few cases it has been marked. (*See* Balser, Case 3.)

The relationship of neuromyelitis optica to the other demyelinating diseases must remain uncertain until more is known of their ætiology. The present writer shares the view of those who hold that in neuromyelitis optica there are certain clinical and pathological features which distinguish it from other members of the demyelinating group. Neuromyelitis optica is characterized by the combination of severe visual and spinal cord symptoms and signs. These may occur concurrently, or may follow one another at a short or a long interval. Signs of involvement of the brain stem are conspicuous by their absence. The cerebrospinal fluid may be normal, or may show an increase in cells and protein with a normal colloidal gold or benzoin curve. The course of the disease is progressive or remittent, but death occurs in the majority of cases within two years. Recovery, usually with sequelæ, seems possible in a small number of cases. The characteristic pathological feature of the disease is a diffuse demyelinating process, often going on to necrosis, which attacks the optic chiasma, optic nerves and spinal cord, with a relatively poor glial fibre reaction. More rarely there are foci of demyelination which do not show necrosis, and in this type of case the glial reaction may be quite marked. Apart from the rare occurrence of discrete demyelination in the brain stem and an occasional vessel showing perivascular infiltration, there and in the basal ganglia, the rest of the nervous system shows no notable pathological change. If these criteria, clinical and pathological, be applied, then it is possible to regard neuromyelitis optica as an entity distinguishable from the other demyelinating diseases such as Schilder's disease, acute disseminated encephalomyelitis and disseminated sclerosis, in all of which visual loss associated with a myelitis may occur. It is natural to suppose that cases from each of these groups will occasionally be encountered which show features common to more than one of them. For example, the clinical and pathological picture of Schilder's disease is so different from that seen in neuromyelitis optica that no confusion would seem possible. However, in the following case reported by Marinesco, Draganesco, Sager and Grigoresco (1930), there were features common to both conditions. The case was that of a woman aged 21 who, in January, 1929, developed headache and vomiting and pain in the lower limbs, followed a month later by double vision, and later by bilateral blindness. In April there was a rapid development of a right-sided hemiplegia with dysarthria, which improved in the course of a few days. In May, she showed signs of a flaccid paraplegia with retention of urine. The cerebrospinal fluid was normal in all respects. The patient died six months after the onset. The cord showed softening from the 5th to the 9th dorsal segment. The right hemisphere showed no lesion. The left hemisphere showed two extensive areas of degeneration, greyish-yellow in colour, and spongy in consistency. They were both confined to the white matter. The one occupied the white matter of the occipital lobe with an extension towards the occipital horn of the lateral ventricle, and even invading the left half of the splenium of the corpus callosum. The other lesion was situated in the centrum ovale beneath the parietal and ascending frontal convolution. The chiasma showed extensive demyelination of its central portion, and in addition there was demyelination close up to the nerve head on the left side. The author's comment on certain features of the case which are characteristic of Schilder's disease, the hemiplegia and the distribution of the lesion in the left hemisphere, although an unilateral effect, is unusual in this disease. The occurrence of a myelitis suggest neuromyelitis optica, and the pathological findings in the chiasma and left optic nerve also favour this diagnosis. They comment on the rarity of spinal cord lesions in Schilder's disease, but refer to the case published by Stewart, Greenfield and Blandy (1927), where cord lesions were found. The authors find in their case a link between neuromyelitis optica and Schilder's disease, but consider that their case comes into the category of neuromyelitis optica. Until we have further knowledge of the ætiology of the demyelinating diseases, it may be impossible to classify such a case as this one.

Certain of the acuter cases of disseminated sclerosis may resemble neuromyelitis optica. However, disseminated sclerosis is as a rule more widespread through the central nervous system, giving rise to a variety of signs that are usually absent in neuromyelitis optica, such as euphoria, ocular pareses, nystagmus, and the other signs associated with disturbance of the cerebellar and vestibular connections. Although loss of vision occurring in both eyes simultaneously does occasionally occur in disseminated sclerosis, recovery as a rule is more complete than in neuromyelitis optica. In the few instances of disseminated sclerosis personally observed where there has been a degree of permanent blindness in both eyes, the defect has always been in the nature of a large central scotoma, no permanent hemianopic loss such as may occur in neuromyelitis optica having been observed. Neuromyelitis optica tends to produce symmetrical effects on the central nervous system. It is true that at the onset one eye and one lower limb may be affected, but in the course of a few hours, or days, the other eye and leg are involved. This symmetrical picture is explained by the tendency of the pathological lesion to be a diffuse one. In disseminated sclerosis, on the other hand, the disease is frequently asymmetrical in its effects, loss of vision being confined to one eye, or, in a paraplegia, one lower limb may be more paresed than the other. As a rule acute cases of disseminated sclerosis shew a greater capacity for recovery than do cases of neuromyelitis optica, as Brain (1933) has pointed out. Merritt (1934) has analyzed the cerebro-spinal fluid findings in 839 cases of disseminated sclerosis. Seventy-one per cent. showed an abnormal Lange colloidal gold curve. In neuromyelitis optica, on the other hand, the Lange curve is almost constantly normal, despite a not infrequent pleocytosis. It must be admitted, however, that cases are encountered from time to time which show features suggestive of both conditions. For example, instances of acute bilateral retrobulbar neuritis associated, perhaps, with a papillitis, but with no other evidence of disease of the central nervous system, are occasionally encountered. Rarely, an infection of the nasal sinuses may be present to explain the condition. In the remainder the diagnosis would seem to lie between disseminated sclerosis and neuromyelitis optica, although it is possible that a few of these cases may never show any further evidence of disease of the central nervous system. A considerable return of vision and a positive colloidal gold curve in such a case would point to disseminated sclerosis. In other cases no definite conclusion may be reached during the life-time of the patient, although the course of the disease, its distribution in the nervous system as judged by the signs, the frequency of relapses and the degree to which they remit, and, lastly, the findings in the cerebrospinal fluid, may enable a conclusion to be arrived at. Finally, the possibility of death occurring in neuromyelitis optica from a myelitis, before the disease has attacked the chiasma, must not be lost sight of.

There are certain differences in the pathological picture which would strengthen the belief that neuromyelitis optica and acute disseminated sclerosis are separate conditions. As a rule the morbid process is more intense in neuromyelitis optica, necrosis being a relatively common finding, whilst its presence in disseminated sclerosis is quite exceptional and probably an accidental finding. From these facts it is only to be expected that there should be differences in the final histological picture in the two diseases. In disseminated sclerosis there is little tendency for destruction of axis cylinders, although they may undergo degenerative changes, whereas in neuromyelitis optica they may be destroyed. In disseminated sclerosis gliosis is a feature of the disease, whereas in neuromyelitis optica the poor response of the macroglia can be attributed to the destruction of astrocytes in the necrotic process. When gliosis is marked, as a rule, the initial lesion has not been so severe. In neuromyelitis optica the grey matter may be as severely affected as the white matter. As Hassin points out, in disseminated sclerosis there may be cellular infiltration of the anterior horns, but the cells themselves are spared, whereas in neuromyelitis optica they are often destroyed. Lastly, an increase in capillaries, which may occur in certain of the more chronic cases of neuromyelitis optica, is not met with in disseminated sclerosis.

Acute disseminated encephalomyelitis, whether spontaneous or following one of the infectious fevers, shows a clinical picture which, in many respects, is different from that seen in neuromyelitis optica. The lesions are more widespread, and may occur through the hemispheres and brain stem, thus giving rise to signs which do not occur in neuromyelitis optica. Most authorities are agreed that blindness is rare in this condition. The pathological picture is one of scattered foci, of demyelination throughout the nervous system with a distinctly perivascular distribution. Hassin stresses the widespread inflammatory features met with in acute disseminated encephalomyelitis.

Returning to the two cases described in this paper, in Case 1 the diagnosis for a time was in doubt. The patient was shown at a meeting of the Neurological Section of the Royal Society of Medicine under the title "Myelitis with Blindness: Acute Disseminated Encephalomyelitis." The clinical picture, the course of the illness, and the results of the pathological examination, are so similar in the two cases, that there can be no doubt that they were affected by the same disease. Judged by the criteria discussed in the previous paragraphs, a diagnosis of neuromyelitis optica seems justified. Speculation as to the reason why these identical twins should suffer the same rare disease of the nervous system is scarcely warranted, in view of our ignorance as to its causation. Assuming, however, that the changes in the nervous system in neuromyelitis optica are due to a virus or its toxin, two possibilities suggest themselves: (1) That each of them had harboured the virus for some years before the nervous system was attacked; or (2) that Case 2, who frequently visited her sister during the latter's illness, was infected by her. It seems likely that if a lowered resistance to disease of the nervous system was inherited, it would be shared by both, in view of their relationship.

I am indebted to Professor J. McIntosh for the facilities he afforded me in the Bland-Sutton Institute of Pathology.

SUMMARY.

(1) The clinical and pathological features of neuromyelitis optica as it occurred in identical twins are described.

(2) These two cases support the view that there is sufficient justification for regarding neuromyelitis optica as a distinct member of the demyelinating group of diseases.

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DISTURBANCES OF SENSIBILITY IN DYSTROPHIA MYOTONICA.

BY OTTO MAAS.

(From the National Hospital, Queen Square)

In the majority of accounts of dystrophia myotonica nothing is said with regard to sensibility in this malady. Curschmann (1936) states that no disturbance of sensibility is to be observed. Rouquès (1931) recorded sensory changes as a rare, and, as he thought, an unimportant exception.

During the course of a study of dystrophia myotonica, the present writer found on the routine testing of vibration sense by the tuning fork that, as compared with the normal subject, this mode of sensibility seemed sometimes impaired in the subject of dystrophia myotonica. However, the absence of satisfactory quantitative standards of acuity of this mode of sensibility made the evaluation of this observation difficult. A quantitative investigation was therefore attempted, and its results are here recorded.

Method of examination.—An apparatus devised by Newman and Corbin (1936) was employed. It consists of an electromagnetic vibrator with a frequency of 300 cycles per second. By means of suitable meters, the threshold of vibration perception in milliwatts can be recorded, the instrument resting by its own weight on chosen sites: namely, the ulnar styloid process, the tibial tuberosity and the internal malleolus.

In the subjects examined the observations were made for me with this instrument by Dr. H. W. Newman, to whom I express my warmest thanks.

Observations and results.—A normal standard was obtained by a series of observations upon eight healthy subjects ranging in age from 26 to 34 years.

In a series of twenty-two patients suffering from dystrophia myotonica, their ages ranging from 13 to 35 years, fourteen showed an acuity of vibration sense less than that of the least acute normal control. This impairment was greatest at the wrist and less at knee and ankle.

Six patients suffering from dystrophia myotonica between the ages of 49 and 55, when compared with a single normal control aged 63, all showed vibratory acuity less than a third of normal at the wrist, while three of them showed diminished acuity at ankle and knee as well.

TABLE

	Name	Sex	Age	Vibration-sense			Myotonia	Muscle-atrophy
				Ulna	Tibia	Malleolus		
1	D.-B.	Female	26	—	—	—	Mild	Mild
2	F. F.	Male	33	—	—	—	Mild	Mild
3	D J.	Female	18	—	—	—	Doubtful	Doubtful
4	T W.	Female	21	—	—	—	Marked	Marked
5	T. B.	Female	22	—	—	—	Mild	Mild
6	G B.	Male	24	—	—	—	Mild	Mild
7	A. B.	Male	28	—	—	—	Marked	Mild
8	T. B.	Male	25	—	—	—	Mild	Mild
9	R G.	Male	32	XXX	X	XXX	Marked	Marked
10	G. J.	Female	17	XXX	X	X	Mild	Mild
11	G. C.	Female	21	XXX	—	X	Mild	Mild
12	L. F.	Female	27	XXX	X	X	Mild	Mild
13	F. J	Male	26	XXX	X	—	Mild	Mild
14	B. J.	Male	24	XXX	XXX	XX	Mild	Mild
15	C. D.	Male	35	XXX	XXX		Mild	Mild
16	J. M.	Male	28	XXX	XXX	X	Very marked	Very marked
17	J G.	Male	35	XXX	—	—	Very marked	Mild
18	D. D.	Female	25	XXX	—	—	Doubtful	Doubtful
19	F. H	Female	19	XXX	XXX	XXX	Doubtful	Doubtful
20	E. H.	Female	22	XXX	X	X	Doubtful	Doubtful
21	L. R.	Female	13	XX	X	X	Mild	No atrophy
22	H C.	Male	35	XXX	XX	XX	Marked	Marked

The sign — denotes vibratory-acuity within normal limits ; X, decreased up ½ of normal, XX, from ½-⅓ of normal ; XXX, less than ⅓ normal acuity.

No constant relationship was found between the severity of myotonia and muscular wasting on the one hand, and the presence or degree of impairment of vibration sense on the other. Of the 22 subjects in the table only three (2, 7, 17) were in hospital on account of weakness or myotonia, the remainder were discovered in the course of a routine investigation of families of persons suffering from dystrophia myotonica and in hospital for this reason.

It appears then that in this series of myotonic subjects about two-thirds presented signs of impaired vibration sense. In all these, routine investigation of cutaneous sensibility (tactile and painful) revealed no abnormality. The subsequent examination of three subjects suffering from well-developed dystrophia myotonica and impairment of vibration sense revealed a normal threshold of tactile sensibility to testing with von Frey's hairs, and a normal threshold to cutaneous pain sense.

At what point in the sensory pathway the conduction of impulses subserving the vibration sense is interfered with is not known. So far, histological examination of the nervous system in dystrophia myotonica has thrown no light on this point. Steinert (1909) reported degeneration in the posterior columns of the cord in one case. In two cases some degeneration of the nerve cells was found in the lateral cell column in which the spinocerebellar tract is believed to arise, but the fibres of this tract were not degenerated, and no relation can be established between this nerve cell lesion and impairment of vibration sense. (Bielschowsky, Maas, Ostertag, 1933.) (Keschner and Davison, 1933.)

Dr. Greenfield kindly examined histologically a cutaneous nerve removed during life from the outer side of the foot in a subject with impaired vibratory acuity at the ankle and suffering from dystrophia myotonica. The examination revealed a perfectly normal nerve.

Although in the series already discussed no impairment of any mode of cutaneous sensibility was observed, the routine examination of a large number of cases of dystrophia myotonica did reveal abnormalities in seven instances. These consisted in areas of tactile hypæsthesia, hypalgesia to pin-prick, or of hypotherm-anæsthesia—either associated or separately—in the distal segments of the limbs. In some cases the entire hand was thus affected. These changes were not of severe degree. Many of these examinations were made under unfavourable conditions, as for example in the patients' homes, and it is possible that more rigorous investigation might reveal a greater frequency of these sensory abnormalities than has been found.

A review of the literature of the disease yields numerous passing references to sensory anomalies. Thus, the presence of spontaneous pains and of paræsthesiæ (" pins and needles ") are recorded by Rossolimo (1902), Pelz (1907), Batten and Gibb (1909), Buzzard (1909), Hirschfeld (1925), Bregman and Potok (1932), Curschmann (1936). Pelz also cites other writers in his paper.

Hypoæsthesia to pressure is recorded by Baake and Voss (1917), Rossolimo (1902) and Pelz (1907).

Diminished sensibility to touch, pain and thermal stimuli, either singly or together, are recorded by Curschmann (1936), Nischau (1920), Scharnke and Full (1920), Steinert (1909), Berg (1904), Gökay (1936), Lortat-Jacob and Thaon (1905).

Disturbance of postural sensibility is recorded by Curschmann (1936) and Rohrer (1916).

This list is probably incomplete, but the results of my own examinations together with the references given suggest that the view held by some authors that these sensory changes are hysterical in nature is not tenable.

Whether these changes derive from peripheral or central nervous changes cannot be determined in the present state of knowledge.

CONCLUSION.

Disturbance of vibration sense is a sign observed in many cases of dystrophia myotonica. In consequence of its frequency we may regard it as an integral part of the symptom complex.

Other signs of disturbed sensibility arise much less frequently. However, they occur in a sufficient number of cases to make it unlikely that they are the result of any affection complicating dystrophia myotonica.

The frequency of signs of sensory change in dystrophia myotonica suggests that this malady is not solely the result of an affection of the muscles themselves.

The author expresses his thanks to the honorary staff of the National Hospital, Queen Square, and to Dr. W. A. Spence of St. Bartholomew's Hospital for permission to examine the cases which form the basis of this paper.

The investigation was carried out under a grant from the Medical Research Council.

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NOTICES OF RECENT PUBLICATIONS.

Meningiomas: Their classification, regional behaviour, life history, and surgical end results. By HARVEY CUSHING, with the collaboration of Louise Eisenhardt. Baltimore: C. H. Thomas. 1938. Pp. 785. Figs. 685.

The differential diagnosis, pathological and topographical, of intracranial tumours has made remarkable strides in the last few years, and no student of the subject can be unaware of the share in this progressive refinement of diagnosis that neurologists owe to Harvey Cushing and his collaborators. A steady flow of monographs and papers have come to us from this source, and the present exhaustive analysis of the symptomatology, behaviour and treatment of the meningiomas is a worthy member of a unique series. The complete and orderly presentation that the reader has learned to expect from Harvey Cushing is here, and proves—if proof were needed—that the field of clinical observation still offers a rich harvest to those who work in it.

The Physiology of the Nervous System. By J. F. FULTON. London: Oxford Medical Publications. 1938. Pp. 630. Figs. 94. Price 25s.

This book is addressed to students of medicine "who must bridge the gap between the concepts of neurophysiology and the problems of clinical neurology."

It may truly be said that the facts of clinical observation for the seeing eye often throw light upon the normal physiology of the nervous system, and in so doing amplify and extend the experimental work of the physiologist. Any exposition of neurophysiology that will facilitate this process will be valuable to workers in both fields, but we may in this connexion more accurately speak of co-ordinating these two orders of observation than of bridging gaps.

Of its nature the task that the author has courageously undertaken is as difficult for the physiologist as for the clinician. The former is writing for someone with whose problems he has no first-hand acquaintance and cannot therefore achieve the selection of what is relevant and useful, nor present this in the most appropriate manner and with the proper emphasis. The latter lacks the personal experience of experimental methods and of the reactions of the experimental animal which are necessary if he is to assess and apply what the physiologist has to tell him.

In the writing of such a book the counsel of perfection indicates a collaboration between physiologist and clinical neurologist, and we may regret that Professor Fulton has not availed himself of a collaboration of this order, for it was surely available.

The lack of it is most clearly seen in the remote and inadequate treatment of the physiology of sensation, but it is evident here and there throughout the book.

Nevertheless, this may be used as a quarry from which the neurologist may dig what he wants, and in his search he is aided by a vast bibliography of some 1,300 papers and a number of clear diagrams.

The Pituitary Gland: An investigation of the most recent advances. Association for Research in Nervous and Mental Diseases. Volume XVII, 1938. London: Baillière, Tindall, and Cox. Pp. 764. Figs. 160 and 50 Tables. Price 45s.

The scope and plan of this volume will be familiar to those who have seen its predecessors in the series. It is divided into three sections, anatomical, physiological and clinical, and provides an exhaustive summary of present knowledge of its subject. Each chapter is followed by a bibliography.

Das Zwischenhirn und die Regulation von Kreislauf und Atmung. Beitrage zur Physiologie des Hirnstammes. II ter. Teil. By W. R. Hess. Leipzig: G. Thieme. 1938. Pp. 125. Price RM. 32.

Employing the method of electric stimulation of deeply-placed points in the brain stem by means of a stereotaxic instrument, a method described in the first part of these "Beiträge," the author describes a series of experiments designed to reveal the nervous control of the circulation and of respiration by the brain stem, and to identify the structures—nuclei and paths—concerned in this regulation.

A long historical review precedes the descriptive experimental matter which comprises the bulk of the monograph.

The Adrenal Cortex and Intersexuality. By L. R. Broster, Clifford Allen, H. W. C. Vines, Jocelyn Patterson, Alan W. Greenwood, G. F. Marrian, and G. C. Butler. With a foreword by Sir Walter Langdon-Brown. Demy 8vo. Pp. 245, with numerous illustrations and charts. London: Chapman and Hall. Price 15s. net.

A book compounded by no less than seven authors, approaching a subject of profound interest and importance from clinical, psychological, pathological, and bio-chemical angles.

The outstanding feature of the publication is the correlation of virilism and sexual disturbances with histological variations within the adrenal cortex and the associated excretion within the urine of specific bio-chemical substances. The histological change is apparent in a fuchsinophil staining of cells of the adrenal cortex. It is a little strange, perhaps, that some of the cases which depict most histological evidence of virilism fail to exhibit free male hormone in the urine.

Numerous clinical cases are cited in illustrating the four groups into which the authors have arranged their cases. The groups consist of: prepubertal virilism, postpubertal virilism, Achard-Thiers Syndrome, and postmenopausal virilism. The cases in the first two of these groups are benefited by surgery, the other groups are best treated by glandular therapy. Particular attention is drawn to the importance of the early instigation of treatment owing to the protracted influences underlying such changes, and the permanence of the induced characteristics.

The diagnosis is somewhat difficult, so much so that laparotomy is advised to this end; perhaps somewhat lightly, as when recommended in children presenting hypertrophic change in the clitoris. Laparotomy is essential to the exclusion of disorders of other glands, to ensure the presence of both suprarenals and determine which is the larger, to exclude the presence of accessory suprarenals, and in order to investigate the state of development of the internal genitalia. The post-operative period is apt to be stormy, hence the operation of adrenalectomy demands good physical resources on the part of the patient.

The results of operation are said to indicate a general and immediate tendency to lose acquired male characteristics with return to normal sexuality psychologically: these results, however, do not appear to be quite so obvious in some of the contained case reports. Hirsutism, although diminished, appears to persist in varying degrees, necessitating depilation by the patient. (Group 1 cases observed after a period of ten years are reported thus: "can control their hirsuties and though they have not menstruated or changed much progress of the disease appears to have been arrested.")

The pathological study is a valuable and commendable contribution to the knowledge of adrenal function in its mechanism of control of sexual development Some of the suggestions are hypothetical. It is disappointing to note that in advocating the application of the pre-operative free hormone test such was not adhered to for "owing to the time taken to perform it it has not been utilised in this series." The section deals very clearly with the relationship of the suprarenal to Cushing's Disease and like conditions, and the relative parts played by chromosomal and endocrinal factors in the sexual pattern. The bi-sexual qualities of the secretions of the adrenal cortex explain the instability of the female sexuality relative to that of the male.

The illustrations are excellent but additions could be made with advantage showing the macroscopic and microscopic changes in the adrenals.

The book is thoroughly recommended to all interested in the endocrinology of sexual function and development.

A Biological Approach to the Problem of Abnormal Behaviour. By Milton Harrington, M.D. Lancaster (U.S.A.): Science Press Printing Company. 1938. Pp. 459.

Like other serious attempts to take the "fundamental facts of anatomy, physiology, medicine and general biology, together with the facts of normal and abnormal psychology, and to build a theory which will harmonize with this large and widely diversified group of facts," Dr. Harrington's book is more easily praised for the purity of its intentions than for the success with which they have been carried out. The cause of the author's failure lies not so much in himself as in the incompleteness of his material: the time for a full synthesis is not yet. Disapproving entirely of the psychoanalytical doctrine, which he criticizes effectively, he has aimed at a mechanistic view of the behaviour of man as a social organism. The outcome is a broad, theoretical survey, acceptable enough and even valuable until we go beyond the surface outlines of abnormal psychology to consider the details of conduct, especially in mental disorder. It also falls short in its grasp of the physiology of the nervous system, as now conceived, and of modern psychology. It is, however, clearly written, interesting, and well designed.

Some Investigations into the Physiology of Emotions. By H. I. SCHOU, M.D. London: Humphrey Milford. 1937. Pp. 111. Price 8s.

So painstaking an investigation as this into some bodily concomitants of mild emotion is particularly valuable now that psycho-somatic relationships are being widely assumed and discussed. With neurotic patients as his subjects, Dr. Schou studied blushing, skin temperature, basal metabolic rate, insensible perspiration, gastric secretion, blood sugar curve, and adrenalin content in the blood. Although the technical procedures are not always those best suited to the inquiry, the findings seem reliable and instructive as far as they go. Whether these observations on weak transient emotional changes in neurotic persons can be extended and applied to the more lasting affective anomalies is questionable. There is, moreover, in this report hardly enough emphasis on the still unaccountable wide individual differences in the physiological manifestations of emotion.

Schizophrenie und Mord: Ein Beitrag zur Biopsychopathologie des Mordes. By Dr. NIKOLA SCHIPKOWENSKY. Berlin: Springer. 1938. Pp. 186. Price RM. 18.

The value of this monograph lies chiefly in the sixteen case-reports, withdrawn from the records of the Munich psychiatric clinic. They serve as the text for a discursive " contribution on the biopsychopathology of murder," much of which is polemical and designed to show how untenable are the views of Lombroso and of Freud. The writer's own conclusions are so vague, expressed as they partly are in terms of " fundamental dynamics of primitive psychic structures," " the specific human instinct of striving after happiness," " the fundamental experience of association between individual, genus, and cosmos," &c., as to be too obscure for examination. The clinical psychiatric comments and the observations on suicidal tendencies in these patients are informative, and the opening sections on biological and anthropological issues interesting but superficial. A rather irrelevant chapter deals with the problem of dreams in relation to psychosis and murder.

Die Psychologie und Psychopathologie der Hysterie. By Dr. ROBERT FLINKER. Leipzig: Thieme. 1938. Pp. 63. Price RM. 4·20.

This is yet another attempt to explain hysteria, in which the author does not bring forward original observations but only his re-arrangement of current views (especially those of Kretschmer), and selects from books he has read evidence to support his belief that an anomaly of purposeful activity is at the root of hysteria. In spite of much detail, the treatment of the subject is superficial, and more suited to an essay than to a monograph.

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